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SUPERIOR COURT OF THE STATE OF CALIFORNIA
FOR THE CITY AND COUNTY OF SAN FRANCISCO

THE PEOPLE OF THE STATE OF CALIFORNIA; AMERICAN CANCER SOCIETY, CALIFORNIA DIVISION; AMERICAN HEART ASSOCIATION, CALIFORNIA AFFILIATE; CALIFORNIA MEDICAL ASSOCIATION; and CALIFORNIA DISTRICT OF THE AMERICAN ACADEMY OF PEDIATRICS, Plaintiffs,	Case No. 980864
vs.	
PHILIP MORRIS, INC.; R.J. REYNOLDS TOBACCO COMPANY; BROWN & WILLIAMSON TOBACCO CORPORATION; B.A.T. INDUSTRIES P.L.C.; LORILLARD TOBACCO COMPANY; LIGGETT GROUP, INC.; THE AMERICAN TOBACCO COMPANY; THE COUNCIL FOR TOBACCO RESEARCH -- U.S.A., INC.; and THE TOBACCO INSTITUTE, INC., and DOES 1-100, inclusive, Defendants.	

VIDEOTAPED DEPOSITION OF A. WALLACE HAYES, a witness called on behalf of the Plaintiffs, taken pursuant to the California Rules of Civil Procedure, before Nancy M. Kingsbury, Registered Professional Reporter and Notary Public in and for the Commonwealth of Massachusetts, at the Offices of Brown, Rudnick, Freed & Gesmer, One Financial Center, Boston, Massachusetts, on Wednesday, June 3, 1998, commencing at 11:46 a.m.

PRESENT:

Lieff, Cabraser, Heimman & Bernstein
(by Michael Sobol, Esq.)
Embarcadero Center West, 275 Battery Street, 30th Floor, San Francisco, CA 94111, for the Plaintiffs.

Womble, Carlyle, Sandridge & Rice
(by Marilyn R. Forbes, Esq., and Martin L. Holton, III, Esq.)
Suite 2100, 150 Fayetteville Street Mall, Post Office Box 831, Raleigh, NC 27602, for the Defendant R.J. Reynolds Tobacco Company.

Climaco, Climaco, Lefkowitz & Garofoli Co., L.P.A.
(by Jack D. Maistros, Esq.)
Ninth Floor, The Halle Building, Cleveland, OH 44115, for Plaintiffs in the five New York State actions, Rose Frosina, Catherine Zito, Phyllis Small, Mary Ann Hoskins and Sharlene Hoberman.

Daly, Kehoe & Crosson, L.L.P.
(by John F. Kehoe, Esq.)
285 Summer Street, Boston, MA 02210, for the Deponent.

ALSO PRESENT: David Sebestyen, Videographer, Jones Communications Group

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EXHIBITS

EXHIBITS

PROCEEDINGS

THE VIDEOGRAPHER: This is Videotape No. 1 in the deposition of A.W. Hayes in The People of the State of California vs. Philip Morris, cross-noticed
11:46:26 in five New York State actions.

Today's date is June 3, 1998, and the time is approximately 11:46 a.m. My name is Dave Sebestyen, and I represent Jones Communications Group located here in Boston at 59 Temple Place.
11:46:48 The telephone number is (617) 542-0039.

This deposition is taking place at Brown, Rudnick, Freed & Gesmer at One Financial Center in Boston, and it was noticed by the Plaintiffs.

11:47:00 At this time if counsel would please introduce themselves for the video record, stating your name, the firm you work for and who you represent in this case.

MR. SOBOL: My name is Michael W. Sobol
11:47:08 from the law firm of Lieff, Cabraser, Heimann & Bernstein, L.L.P., in San Francisco, California. I'm here on behalf of the Plaintiffs in The People of the State of California vs. Philip Morris, et al.

11:47:22 MR. MAISTROS: My name is Jack Maistros with the law firm of Climaco, Climaco, Lefkowitz & Garofoli in Cleveland, Ohio, here on behalf of the Plaintiffs in the New York State actions. Specific
11:47:34 captions, of which we, I think you will agree, there are five of them, and I will read into the record if required.

MR. HOLTON: My name is Martin Holton of the Winston-Salem law firm of Womble, Carlyle
11:47:48 Sandridge & Rice. I'm here on behalf of R.J. Reynolds Tobacco Company.

MS. FORBES: Marilyn Forbes from the same firm, here on behalf of R.J. Reynolds Tobacco Company.

11:47:54 MR. KEHOE: My name is John Kehoe. I'm with the Boston firm of Daly, Kehoe and Crosson, L.L.P. I'm here on behalf of the deponent, Dr. Wallace Hayes.

THE VIDEOGRAPHER: At this time the court
11:48:04 reporter will swear in the witness.

A. WALLACE HAYES

a witness called for examination by counsel for the Plaintiffs, being first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. SOBOL:

Q. Good morning, sir.

A. Good morning.

11:48:20 Q. We had a chance to briefly introduce ourselves before the deposition. Why don't you state your name for the record, sir.

A. My name is A. Wallace Hayes.

Q. I'm Michael Sobol. I represent the
11:48:30 Plaintiffs in tobacco litigation pending against your former employer, R.J. Reynolds, and other companies. Do you understand that?

A. Yes.

Q. Where do you live, sir?

11:48:40 A. [DELETED]

Q. What is your address there?

A. [DELETED]

Q. Have you got any plans on moving in the near future?

11:48:50 A. No.

Q. Have you ever had your deposition taken before?

A. Yes.

Q. More than once?

11:49:00
A. No.
Q. When was the last time you had your deposition taken?
A. I don't remember the date, but it was in
11:49:10 the past 15 months.
Q. Do you know why you were deposed at that time? What was that in connection with?
A. (Witness shakes head)
Q. What were you deposed in connection with?
11:49:22 Do you know that?
A. Some litigation, but I'm not sure which one.
Q. Was it involving the tobacco companies?
A. Yes.
11:49:36 Q. And you testified regarding your former employment at R.J. Reynolds?
A. I just answered the questions that were asked to me.
Q. You used to work for R.J. Reynolds?
11:49:48 A. Yes.
Q. When did you start?
A. 1984, I believe.
Q. Are you still working there?
A. No.

11:50:08 Q. When did you leave?
A. 1992.
Q. Why did you leave?
A. I was fired.
11:50:18 Q. Why were you fired?
A. A new person came in to run the department I was in, and he told me that he wanted to develop his own people.
Q. Who was this new person that came in?
11:50:32 A. Carl Ehman.
Q. "Karl" with a "K"?
A. I don't know.
Q. What department?
A. Research and Development.
11:50:48 Q. What was your position in 1992 when you were let go by R.J. Reynolds?
A. Vice president, Biochemical Biobehavioral Group.
Q. Do you know who became vice president of
11:51:08 the Biochemical Biobehavioral Group after you were fired?
A. If my memory serves me correctly, no one.
Q. It's your understanding that that position was eliminated?

11:51:18 A. That's my understanding.
Q. Did you receive a pension from R.J. Reynolds?
A. Yes.
11:51:30 Q. Is that on a monthly basis?
A. Yes.
Q. What is your monthly pension from R.J. Reynolds.
(Attorney-client conference)
11:51:54 A. $315.85 gross -- net. I'm sorry, net.
Q. Are you represented by anyone here today?
A. Yes.
Q. That's Mr. Kehoe?
A. Correct.
11:52:10 Q. Are you paying for his services?
A. No.
Q. Who is?
A. I assume that R.J.R. is.
Q. How is it that you found Mr. Kehoe?
11:52:24 A. He was -- he called me and told me that he would represent me.
Q. In connection with this particular deposition?
A. Yes.

11:52:40 Q. When was the first time you met Mr. Kehoe? Did you meet him through R.J. Reynolds?

A. I met him for the first time when I was deposed earlier.

11:52:52 Q. And R.J. Reynolds suggested that you get in contact with Mr. Kehoe that first time?

A. He got in contact with me.

Q. You are aware, sir, that R.J. Reynolds, during the time that you were an employee there,

11:53:18 were selling cigarettes in the State of California?

A. Yes.

Q. And that those cigarettes were intended for consumption by California residents?

A. Yes.

11:53:36 Q. Do you have an understanding that R.J.R. derived substantial revenue from the State of California by virtue of its sale of cigarettes?

A. I have no idea how much revenue.

Q. You would expect it to be in the millions

11:53:56 of dollars, wouldn't you?

MS. FORBES: Objection. Asked and answered.

A. Not being in the marketing area, I have no idea.

11:54:02 Q. You wouldn't be able to make that assessment sir?

MS. FORBES: Objection. Asked and answered.

11:54:08 A. I just don't know.

Q. All right, sir. I'm going to ask you a bunch of questions today regarding your former employment at R.J. Reynolds, and I want to make sure that you understand my questions. So if you don't

11:54:22 understand my question, you just let me know. I can try to rephrase it for you, I can speak up. Sometimes I mumble, sometimes I don't make sense, so if you don't understand my question, I want you to

11:54:36 tell me because I don't want you answering a question you don't understand. Is that fair?

A. Good.

Q. You understand that?

A. Uh-huh.

Q. If at any time you need to consult with

11:54:44 your lawyer as you did just a moment ago, you let me know and we'll break. And if at any time we need to take a break in the session, go off the record, just let me know, okay?

You understand that you are here under

11:54:56 oath?

A. Yes.

Q. And you are here to tell the truth?

A. Yes.

11:55:02 Q. And if a response to one of my questions would mean providing information that may be detrimental to your former employer, that wouldn't stop you from telling the truth, sir?

MS. FORBES: Objection.

11:55:12 A. It would not.

Q. It would not?

A. It would not.

MS. FORBES: That's unfair. He is here to tell the truth.

11:55:30 Q. What was your position with R.J. Reynolds when you started in about 1984?

A. Director, Biochemical Biobehavioral Group.

Q. And how is it that you got a job at R.J.R.?

11:55:52 A. A headhunter called me.

Q. Do you remember who that was?

A. No.

Q. Where were you working at the time?

A. In Philadelphia.

11:55:58
Q. With whom?
A. Rohm and Haas.
Q. Do you remember what that headhunter said to you?
11:56:08
A. That he had a job that I might be interested in.
Q. Did he describe the job at R.J.R. to you?
A. Not initially there.
Q. At any time did the headhunter describe the
11:56:18
job to you at R.J.R.?
A. Yes.
Q. How did this headhunter describe the job?
A. As a job to work on a concept that I later found out to be Premier.
11:56:38
Q. How did he describe this concept? Is that what you referred to it as, a concept?
A. A concept, Premier, correct.
Q. How did he describe this concept to you?
A. It was basically a new approach to
11:56:56
developing a cigarette that would have less smoke, less smoke.
Q. Did you go down to Winston-Salem to meet some folks from R.J.R. about the job prospect?
A. Yes.

11:57:12 Q. Do you remember who you met with?
A. Bob Di Marco, Gerald Long, and a number of people at R&D, and I couldn't tell you who they were.
11:57:30 Q. Is that because they are no longer there or were no longer there when you started the -- let me rephrase the question.
MS. FORBES: Objection.
Q. Is it that you don't recall because those
11:57:40 persons were not employed at R.J.R. at the time you started?
A. I just don't recall.
Q. Did you meet with Bob Di Marco in person?
A. Yes.
11:57:56 Q. Can you describe what your job responsibilities would be in this position.
A. Yes.
Q. And what did he tell you?
A. He told me that I would head up a group
11:58:08 called Biochemical Biobehavior.
Q. Did he give you any more details as to what that might entail, sir?
A. That it would be involved with this concept of Premier.

11:58:20 Q. Did he describe to you the Premier concept at that time?

A. Yes.

Q. What did he tell you about Premier?

11:58:30 A. He told me that it was a concept that they had been working on to develop a cigarette that would produce less smoke.

Q. Did he give you any more detail than this headhunter gave you?

11:58:42 A. Yes.

Q. Do you recall what that detail was?

A. No.

Q. Did he describe any job responsibilities as the director of -- that the director of Biochemical Biobehavioral might have other than a connection

11:58:58 with the Premier project?

A. Yes.

Q. What did he tell you in that regard?

A. He told me that it would involve the

11:59:14 Regulatory Group, and if I remember correctly, the Occupational Hygiene Group.

Q. Anything else that you recall?

A. No.

Q. What is the Regulatory Group?

11:59:44 A. This would be the group that would interact with regulatory agencies, Environmental Protection Agency, et cetera.

Q. For what purpose?

12:00:02 A. To meet those regulatory requirements that would encompass the things that R.J.R. did.

Q. Did that include working with the F.D.A.; do you recall?

A. Later on it did.

12:00:28 Q. But that's not what you and Dr. Di Marco talked about at the time you were interviewing with him?

A. I don't remember.

Q. And you also met with Gerald Long?

12:00:36 A. That's correct.

Q. What was Gerald Long's position when you -- at the time you met with him?

A. He was president and CEO.

Q. And what did you talk to him about?

12:01:00 A. Just general topics of having to do with those things that people talk about over dinner.

Q. Did you talk about the nature of the work that you would be doing at R.J.R. with Mr. Long?

A. I don't remember.

12:01:14 Q. Did you talk about the Premier project with Mr. Long?

A. I don't remember.

Q. Did you talk about issues involving

12:01:26 environmental tobacco smoke with Dr. Di Marco at the time you were interviewing with him?

A. No.

Q. What about with Mr. Long; did you talk with him about that?

12:01:34 A. I don't remember.

Q. Did you make just the one trip down to Winston-Salem in connection with landing your job with R.J.R.?

A. I made more than one trip.

12:01:50 Q. Did you meet with Dr. Di Marco and Mr. Long in that first trip?

A. I don't remember which trip it was when I met with Mr. Long.

Q. You met with Dr. Di Marco every time you

12:02:04 went down to Winston-Salem to interview for the job?

A. Yes.

Q. And in all these trips that you made, do you remember anyone else that you talked to?

A. No.

12:02:14 Q. What was your position at Rohm and Haas, and can you spell those names for the court reporter.

A. R-o-h-m, and, a n d, H-a-a-s.

12:02:28 Q. What were you doing with them at the time that you began at R.J.R.?

MS. FORBES: Objection.

A. I did nothing with them when I began at R.J.R.

12:02:38 Q. At the time, what was your position when you left Rohm and Haas?

A. I was director, Agriculture, Regulatory Worldwide.

Q. What did your job responsibilities entail as the director of Agriculture and Regulatory

12:02:56 Worldwide?

A. To develop a department at Rohm and Haas which would interface with regulatory agencies around the world.

12:03:16 Q. Interface with regulatory agencies for what purpose?

A. Registration, registration of pesticides.

Q. What kind of business was Rohm and Haas in at the time?

12:03:32 A. Specialty chemicals.
Q. How long had you been with them?
A. Five years.
Q. Beginning at about 1979?
12:03:46 A. '79, '80.
Q. Did you hold the same position the entire time you were there?
A. No.
Q. What was your position before you were
12:03:58 director of Agriculture and Regulatory Worldwide?
A. Director, Toxicology Research.
Q. What did you do as a director of Toxicology Research?
A. Ran the toxicology laboratory at Rohm and Haas.
Q. What did the lab do, generally speaking?
A. Did research and testing for all of Rohm and Haas's products that needed safety evaluation.
Q. Such as what products?
12:04:40 A. Blazer, herbicide; Kathon, a biocide.
Q. Was it one of the goals of the toxicology research lab at Rohm and Haas to determine if the chemicals were safe for human handling?
MS. FORBES: Objection. Vague.

12:05:08 A. It was the purpose to evaluate whether or not the product was considered to be safe.

Q. They had end-agricultural uses, these products?

12:05:22 A. The two that I mentioned have agriculture uses.

Q. Was one of your jobs, then, to determine whether or not they were safe for use as well as for handling?

12:05:36 MS. FORBES: Objection. Vague and ambiguous.

A. You are going to have to help me with "safe."

Q. Okay. What do your toxicology tests show? Let me rephrase. What did the toxicology test show on those two substances which you mentioned?

12:05:52 A. Which toxicology test?

Q. Okay. Why don't you tell me the toxicology tests you used on those two substances.

12:06:08 A. You want me to go through every single test that we used on those two substances?

Q. I'm trying to get --

MS. FORBES: Please let him respond, and it will make the job for the court reporter much easier

12:06:22 if you let the person finish speaking before you jump in.

Q. I'm just trying to get a sense, sir, of what the purpose of the tests were and whether or
12:06:30 not you were just attempting to make sure that product was safe for use as intended, whether or not it was safe for the handling, not necessarily its use.

MS. FORBES: Objection. Ambiguous and
12:06:42 vague.

Q. Do you not understand that?

A. (Witness shakes head)

MS. FORBES: Objection. Argumentative.

Q. Are you having a hard time with that one?
12:06:50 MS. FORBES: Objection. Argumentative. Ask a proper question. He'll respond.

A. Yes.

Q. How long did you run the toxicology lab at Rohm and Haas?
12:07:02 A. About four years.

Q. How many substances would you say you tested in the course of that four years?

MS. FORBES: Objection. Vague.

A. I don't recall.

12:07:18 Q. Other than agricultural uses, did you test products for any other uses?

A. Yes.

Q. What kinds of uses?

12:07:26 A. Military, civilian.

Q. What is a military use?

A. A resin to decontaminate nerve gases.

Q. That's an example of a particular military use?

12:07:52 A. That is what we did on behalf of the military; that's correct.

Q. Was there anything else you did on behalf of the military?

A. Not to my recollection.

12:08:02 Q. What is a civilian use?

A. Polymers and monomers that would be used in making various types of resins and plastics.

Q. Anything else?

A. There probably were, but I don't recall.

12:08:28 Q. What was the purpose of running a toxicology test on the polymers, monomers and resins used for plastics in civilian use?

MS. FORBES: Objection. Overbroad and vague.

12:08:40 A. Again I would have to know which specific use we were talking about before I could answer that question.

Q. Would it be fair to say, sir, that you were 12:08:52 just attempting to see if the product was safe to be used as intended?

MS. FORBES: Objection. Mischaracterizes.

A. Again, it's a specific product.

Q. So --

12:09:04 A. And use.

Q. It wouldn't be the case, then, that with every substance which you tested, you were attempting to determine whether or not it was safe for use as intended?

12:09:16 MS. FORBES: Objection. Mischaracterizes, argumentative.

A. I would say that any test that we did at Rohm and Haas was done to ensure that that product in the form that it was evaluated in was done to 12:09:48 ascertain whether or not it could be, under normal use conditions, be used safely by workers and by consumers.

Q. Did you work with Gary Burger at Rohm and Haas?

12:10:06
A. Yes.
Q. Was he your superior at Rohm and Haas?
A. No.
Q. What was his position?
12:10:16
A. I don't remember his exact title.
Q. What did he do?
A. Pathology.
Q. Did you supervise him?
A. He reported to me.
12:10:38
Q. Was he part of the toxicology lab?
A. Yes.
Q. What about Don DeBethizy; did you know him at Rohm and Haas?
A. Yes.
12:10:58
Q. What was Dr. DeBethizy's title?
A. I don't remember.
Q. Did he work in the Toxicology Lab?
A. Yes.
Q. And did he report to you?
12:11:08
A. I don't remember, but I don't think that he did.
Q. Did you work with anyone else at Rohm and Haas other than Dr. Burger and Dr. DeBethizy that you ended up working with at R.J.R.?

12:11:30 A. Dave Doolittle.
Q. Anyone else?
A. No.
Q. Was Dave Doolittle part of the Toxicology
12:11:42 Lab at Rohm and Haas?
A. Yes.
Q. Did he report to you?
A. No.
Q. Did you report to him?
12:11:54 A. No.
Q. Did you report to DeBethizy?
A. No.
Q. Which of the four of you began to work at
R.J.R. first?
12:12:08 A. I did.
Q. Did you recruit Dr. Burger to join R.J.R.?
A. Yes.
Q. Did you recruit Dr. DeBethizy to join
R.J.R.?
12:12:24 A. Yes.
Q. And Dave Doolittle, is he a "Dr."?
A. Yes.
Q. And did you recruit Dr. Doolittle to join
R.J.R.?

12:12:30 A. Yes.
Q. What was the purpose behind recruiting these three scientists to work at R.J.R.?
MS. FORBES: Objection. Vague.
12:12:42 A. To bring in excellent scientists.
Q. Still in touch with any of those folks?
A. Yes.
Q. When was the last time? Did you talk to Dr. Burger about this deposition?
12:12:58 A. No.
Q. Did you talk to him about the deposition you gave last August?
A. No.
Q. What about Dr. DeBethizy; did you talk to
12:13:06 him about this deposition?
A. No.
Q. Or the deposition that you gave last August?
A. I may have mentioned in passing that I was
12:13:14 deposed.
Q. You have seen Dr. DeBethizy in the time since your last deposition?
A. Yes.
Q. Where was that?

12:13:22 A. Seattle.
Q. What were you doing in Seattle?
A. At a scientific meeting.
Q. Did you discussion it substantively with
12:13:34 him?
A. No.
Q. Did you talk about the tobacco litigation
at all with him?
A. No.
12:13:40 Q. What about Dave Doolittle; are you still in
touch with Dave Doolittle?
A. Yes.
Q. When was the last time you spoke with him?
A. Seattle.
12:13:46 Q. When was the conference in Seattle?
A. March.
Q. March of 1998?
A. Correct.
Q. What were you going to do with these
12:14:00 excellent scientists once they got to R.J.R.?
MS. FORBES: Objection. Argumentative.
A. Whatever their expertise was, to use them
in those areas.
Q. What is Dr. Burger's expertise?

12:14:20 A. Pathology.
Q. What is Dr. DeBethizy's expertise?
A. Pharmacokinetics.
Q. What about Dr. Doolittle; what was his
12:14:32 expertise?
A. Mutagenicity.
Q. And it's on the basis of these expertise
that you recruited them to work at R.J.R.?
A. Yes.
12:14:52 Q. How long were you at R.J.R. before these
folks began working for R.J.R. -- well, we'll take
them one at a time, actually. How long were you at
R.J.R. before Dr. Burger began working at R.J.R.?
A. I don't remember specifically, but it
12:15:08 wasn't long.
Q. A matter of months?
A. Yes.
Q. And would that be true of Dr. DeBethizy as
well?
12:15:12 A. Yes.
Q. And Dr. Doolittle as well?
A. Yes.
Q. Were you going to R.J.R., sir, to set up a
toxicology lab?

12:15:22 A. Yes.
Q. And did this toxicology lab have an intended application beyond the Premier project?
MS. FORBES: Objection. Vague.
12:15:44 A. No -- let me correct that, and the answer would be "yes."
Q. What was the intended application of the toxicology lab at R.J.R. which you were to establish beyond that which involved Premier?
12:16:00 A. The same as we discussed about Rohm and Haas.
Q. Can you state for the record what that other purpose was.
12:16:20 A. To evaluate the safety, toxicity of materials of interest to R.J.R.
Q. Was there any other intended application of the toxicology lab which you were to establish at R.J.R. beyond what you have testified to?
MS. FORBES: Objection. Vague.
12:16:48 A. Not to my knowledge.
Q. Okay. Did you have an expectation when you began working at R.J.R. that your employment would last beyond the Premier project?
MS. FORBES: Objection. Vague.

12:17:06 A. I never really thought about that.
Q. Did you join R.J.R. with the understanding
that you were just to work on the Premier project,
and when the Premier project was done you would move
12:17:16 on to something else somewhere else?
MS. FORBES: Objection.
A. I never really thought about that.
Q. When you were recruiting Dr. Burger,
Dr. DeBethizy or Dr. Doolittle, did you tell them
12:17:30 that they were only going to have employment for as
long as the Premier project was around?
MS. FORBES: Objection. Argumentative.
A. Not to my knowledge.
Q. Did you tell them that this would be
12:17:40 indefinite employment and they were to be hired for
purposes other than that which related to the
Premier project?
A. No more than I would have told anybody
else.
12:17:58 Q. Did you discuss the Premier project with
Dr. Burger when you were recruiting him?
A. Yes.
Q. What did you tell him?
A. That the thing that we were going to be

12:18:14 able to do was develop a cigarette which would have reduced smoke.

Q. How was Dr. Burger as a pathologist going to assist in developing a cigarette with reduced

12:18:36 smoke?

A. You would have to ask him that. That's not my expertise.

Q. You recruited him without knowing how it is that he could participate in the Premier project?

12:18:48 MS. FORBES: Objection. Argumentative.

A. He would participate as a pathologist.

Q. And how would that participation manifest itself?

MS. FORBES: Objection. Argumentative.

12:18:56 A. I'm not a pathologist, and I can't answer that question. I don't know.

Q. What made you think that a pathologist would assist in the Premier project?

MS. FORBES: Objection. Asked and answered.

A. In doing toxicology, a key element is pathology.

Q. What is pathology?

A. The study of the adverse effects of foreign

12:19:38 agents on organs, tissues, cells.

Q. Did you describe the Premier project to Dr. DeBethizy when you were recruiting him?

MS. FORBES: Objection. Asked and answered.

A. Yes.

Q. What did you tell him?

A. That we would be evaluating a cigarette that had reduced smoke.

12:20:30 Q. And what made you think that a pharmacokinetic person would -- strike that. What was your thought behind having someone experienced in pharmacokinetics -- let me try one more time.

What was your thought behind having someone

12:20:54 experienced in pharmacokinetics assisting in the Premier project? How was that going to help?

A. It would allow to verify the reduction in the amount of smoke.

Q. Where is this reduction to take place?

12:21:28 A. What reduction?

MS. FORBES: Objection. Vague.

Q. You said that someone experienced in pharmacokinetics would be able to verify the amount of reduction in the smoke; is that correct?

12:21:38
A. Of the cigarette.
Q. How does pharmacokinetics verify the amount of reduction in smoke in the cigarette?
A. By measuring the amount of the chemicals in
12:21:54 the smoke.
Q. What is pharmacokinetics?
A. The study of xenobiotics in biological systems.
Q. What are xenobiotics?
12:22:20 A. Foreign materials.
Q. So Dr. DeBethizy was to measure the smoke in biological systems?
MS. FORBES: Objection. Misstates and mischaracterizes.
12:22:50 A. To measure the chemicals from the smoke in biological systems.
Q. And the way he was going to verify the amount of reduction of smoke was to use the nicotine metabolites as a marker; is that correct?
12:23:12 A. If my recollection serves me correctly, that was one of several markers that he used.
Q. What were the other ones?
A. I don't recall.
Q. Is it fair to say, then, that Dr. DeBethizy

12:23:36 was going to assist in verifying the amount of reduction in smoke by determining the amount of foreign materials in the human body deposited by virtue of smoking?

12:23:52 MS. FORBES: Objection. Vague and ambiguous.

A. No.

Q. How was Dr. DeBethizy to use the metabolites of nicotine as a marker to determine how much smoke people ingested?

12:24:14 MS. FORBES: Objection. Misstates, vague.

A. I think that you would be best served to ask him how he did it. He has published all that data. It's in the open literature.

12:24:32 Q. What about Dr. Doolittle; you recruited him as well, correct?

A. Correct.

Q. Did you talk to him about the Premier project?

12:24:36 A. Yes.

Q. What did you tell him?

A. Same thing that I told the other two.

Q. That you were evaluating a cigarette with reduced smoke?

12:24:44
A. Correct.
Q. How was a mutageneticist going to help out with that?
A. I assume that you are talking about the
12:25:04 person, a mutageneticist?
Q. How was the study of mutagenicity going to assist in the Premier project?
A. This would also allow to evaluate the reduction of these materials in cigarette smoke.
12:25:24 Q. How was it going to help evaluate the reduction of these materials in cigarettes?
A. Again you need to ask him for the details. And to the best of my recollection, this has all been published too in the open literature.
12:25:38 Q. But in 1984 you had an understanding that Doolittle, who had an expertise in mutagenicity, would assist in the development of the Premier project?
MS. FORBES: Objection. Argumentative.
12:25:46 A. That's correct.
Q. But you don't recall -- do you recall the basis why you thought Dr. Doolittle would experience a mutagenicity would assist with the Premier project?

12:25:58 MS. FORBES: Objection. Asked and answered.

A. It would allow to determine the reduction in materials in the smoke of the Premier cigarette. Again, all of this is spelled out in detail in the open literature.

12:26:12 Q. So you recruited a pathologist, someone experienced in pharmacokinetics and someone experienced in mutagenicity to assist with the Premier project?

12:26:22 A. Correct.

Q. Was it your understanding that R.J.R. was attempting to market a cigarette with reduced compounds of concern?

12:26:32 MS. FORBES: Objection. Vague.

A. We were trying to develop a cigarette that had reduced smoke.

Q. Was the purpose behind reducing the smoke to reduce compounds which were linked to health

12:26:50 issues, health concerns?

MS. FORBES: Objection. Vague.

A. When you reduce the amount of smoke, you take out those chemicals which, through a variety of evaluations, had been suggested to have adverse

12:27:08 effects.

Q. Was it your understanding that R.J.R. was attempting to develop a safer cigarette?

MS. FORBES: Objection. Vague.

12:27:18 A. I'm not sure what R.J.R. was attempting to do. I can tell you what I was attempting to do.

Q. Were you attempting to assist in the development of a safer cigarette on behalf of R.J.R. when you were working in the Premier project?

12:27:30 A. I was attempting to develop a cigarette that had reduced amounts of smoke, and thereby it had reduced amounts of chemicals in it.

Q. The chemicals which you mentioned have been suggested as being linked to certain diseases?

12:27:52 MS. FORBES: Objection. Mischaracterizes.

A. They had been. Some of them had been suggested to be linked to certain diseases.

Q. Were you targeting any of these chemicals in particular?

12:28:08 A. I don't remember the specifics. Again, there's a book on Premier that's 500, 600 pages in length that has all these details in it. I just don't remember.

Q. Where did you work before you were working

12:28:40 at Rohm and Haas?

A. University of Mississippi Medical School.

Q. What were you doing there?

A. I was a professor.

12:28:50 Q. What department?

A. Pharmacology and Toxicology.

Q. How long were you there?

A. Four or five years.

Q. Where were you before that?

12:29:22 A. University of Alabama.

Q. Were you working?

A. Yes.

Q. What were you doing there?

A. Professor. A professor.

12:29:32 Q. What department?

A. Microbiology and Chemistry.

Q. What is pharmacology?

A. The study of the therapeutic effects of chemicals.

12:30:08 Q. Did your experience in pharmacology ever assist you while you were working at R.J.R.?

A. I'm sure it did.

Q. But you don't have any specific recollection of it now, do you?

12:30:20 A. No.
Q. How long were you at University of Alabama?
A. Seven years.
Q. As a full professor the entire seven years?
12:30:36 A. No.
Q. Were you ever a full professor at the University of Alabama?
A. Yes.
Q. Tenured?
12:30:40 A. Yes.
Q. Where were you before that?
A. Vanderbilt University Medical School.
Q. Were you in the medical program as a student?
12:30:56 A. No.
Q. What were you doing at Vanderbilt?
A. I was a postdoctoral fellow.
Q. Studying what?
A. Fungal metabolites.
12:31:10 Q. What are they?
A. Metabolic products produced by common molds.
Q. Where did you get your doctorate?
A. Auburn University.

12:31:30
Q. What year?
A. 1967.
Q. What was your doctorate in?
A. Microbial biochemistry.
12:31:46
Q. What was that first word?
A. "Microbial."
Q. Microbial biochemistry?
A. Correct.
Q. What is microbial chemistry?
12:31:58
A. Biochemistry of microorganisms.
Q. Did you do your undergraduate work at Auburn?
A. No.
Q. Where did you do your undergraduate work?
12:32:14
A. Emory University.
Q. When did you graduate Emory?
A. In 1961.
Q. Do you have a Bachelor of Science there?
A. No.
12:32:22
Q. Bachelor of Arts?
A. No.
Q. What was your degree there?
A. An A.B.
Q. In what?

12:32:34 A. It was biology, chemistry.
Q. Did you start there in the fall of '57?
A. That's sounds about right, yes.
Q. Where did you go to high school?
12:32:52 A. Kaiserslautern American High School.
Q. Where is that?
A. Kaiserslautern, Germany.
Q. Were your parents in the military?
A. Yes.
12:33:18 Q. Where are you working now?
MR. KEHOE: At the last deposition I think I put it on the record, or maybe it was off the record, that I'm perfectly willing to let him answer where he is working, but I'm not going to allow him, 12:33:40 and I will direct him not to answer, any questions in connection with his present work based on my understanding of the Rules of Civil Procedure that it has to be at least likely to lead to the discovery of admissible evidence even under the 12:33:54 broad scope that we are operating under here today. So I will tell you he is working at the Gillette Company, and that's it.
MR. SOBOL: Okay. Well, I'm going to ask him if he does any work relating to cigarettes or

12:34:06 tobacco at Gillette.

Q. And before I get there, you are working at the Gillette Company, sir?

A. Yes.

12:34:14 Q. And you have been working there since you left R.J.R.; is that right?

A. No.

Q. How long have you been working at the Gillette Company?

12:34:22 A. Five years.

Q. Started in 1993?

A. Yes.

Q. What did you do between the time you left R.J.R. and you began working for the Gillette Company?

A. Professor at Wake Forest Medical School.

Q. Doing what?

A. Teaching and research. I was a professor.

Q. What subject?

12:34:50 A. Pharmacology, toxicology.

Q. Any of your research at Wake Forest involve tobacco or cigarettes?

A. No.

Q. And any of your work at Gillette involve

12:35:20 tobacco or cigarettes?

A. No.

Q. Nicotine?

A. No.

12:35:26 Q. Any of your work at Wake Forest involve nicotine?

A. No.

Q. Prior to beginning your work at R.J.R. in 1984, had you done any work in the tobacco- or

12:35:38 cigarette-related --

A. No.

Q. -- fields? The answer after I get my full question out. Sorry.

A. No.

12:35:52 Q. Thank you. Are you familiar, sir, with the F.T.C. smoking method?

A. Vaguely.

Q. What is your understanding of the F.T.C. smoking method?

12:36:02 A. That it's a method that was designed to compare cigarettes.

Q. What does it measure?

A. Tar and nicotine.

Q. Do you have an understanding of whether or

12:36:24 not the measurements it gives for tar and nicotine -- strike that.

How did you gain this understanding of the F.T.C. smoking method?

12:36:38 A. Somewhere along the line I watched the procedure.

Q. While you were at R.J.R.?

A. Yes.

Q. What was the purpose for watching the

12:36:48 procedure?

A. Curiosity.

Q. Was it related to the work you were doing at R.J.R. in any way?

MS. FORBES: Objection. Vague.

12:37:14 A. We did -- people within R.J.R. did the F.T.C. method on Premier.

Q. Premier was test-marketed?

A. Yes.

Q. And F.T.C. values for tar and nicotine were

12:37:36 reported in connection with the test-marketing of Premier?

A. I don't remember.

Q. Other than deriving values to report in connection with the test-marketing of Premier, were

12:37:54 there any other reasons to perform the F.T.C. smoking method on the Premier cigarette that you recall?

MS. FORBES: Objection. Lack of

12:38:00 foundation, misstates.

A. I had said earlier that I didn't recall, so I don't know how to answer the question that you just phrased.

Q. Why did you use the F.T.C. method in

12:38:10 connection with --

A. I don't recall.

Q. Let me get my question out for the record so that we have a clean question and then an answer.

12:38:22 Why is it that you employed the F.T.C. smoking method in connection with Premier?

MS. FORBES: Objection. Misstates.

A. Could you repeat that.

Q. Why is it that the F.T.C. smoking method

12:38:36 was used in connection with the Premier project?

MS. FORBES: Same objections.

A. To compare it to a test cigarette.

Q. Do you have an understanding of whether or not F.T.C. smoking method values are meant to

12:39:08 reflect the average exposure by smoking a cigarette for a human being?

MS. FORBES: Objection. Vague and ambiguous.

12:39:18 A. The F.T.C. -- as I understand it, the F.T.C. method allows comparison of cigarettes for their delivery of nicotine and tar.

Q. Let's take nicotine. Do you have an understanding as to whether or not the value for the 12:39:42 delivery of nicotine derived from -- using the F.T.C. smoking method is meant to be a number which the average smoker would yield by smoking that cigarette?

MS. FORBES: Objection. Vague and 12:39:58 ambiguous.

A. I don't understand "yield."

Q. Do you recall what the nicotine yield was for the Premier cigarette using the F.T.C. smoking method?

12:40:16 A. It's in the book on Premier, and my memory says it was down around the 0.1 milligram level, but I'm not completely certain of that number.

Q. Was it your understanding that if you are right about the 0.1 milligram level, assuming that

12:40:38 to be the case, sir, would it be your understanding that the 0.1 milligram nicotine value derived from the F.T.C. smoking method would be that amount of nicotine delivered to a smoker of a Premier
12:40:52 cigarette?

MS. FORBES: Objection. Vague and ambiguous.

A. Without knowing the correct number, I couldn't answer that question.

12:41:04 Q. Whatever value that you derived for the nicotine yield of the Premier cigarette, would it be your understanding that that value was meant to indicate the amount of nicotine that would be delivered to a smoker of a Premier cigarette?

12:41:20 MS. FORBES: Objection. Vague and ambiguous.

A. That would be delivered, yes.

Q. Why don't you tell me what you mean by "delivered" in that answer.

12:41:54 A. As I understand "delivered," that's the amount of material that comes out of the end of the cigarette.

MS. FORBES: Mr. Sobol, for the record, we were here two hours ago because the deposition was

12:42:18 noticed for 11:00. I understand you had trouble with having the videographer here, but we have now been going for an hour, and Dr. Hayes is on European time. So it looks like you are about ready to
12:42:30 switch subjects. Let's go ahead and take our lunch break now.

MR. SOBOL: Well, that's fine if you want to take your lunch break now. I was actually going to stay on the same subject for a moment, but if you
12:42:38 want your break now, we can certainly have it. Either way.

MS. FORBES: It's up to you if you want to ask a couple of questions and finish this area, that's fine too, but I just want to put you on
12:42:46 notice that we have been here for two hours.

MR. SOBOL: Okay. I understand. Why don't I just mark one exhibit. It's about a paragraph long, and we will get out of here before 1:00, I would think.

12:42:56 MS. FORBES: That's fine.

(Document marked as Hayes Exhibit 1 for identification)

Q. Dr. Hayes, I've had marked as Exhibit No. 1 a document entitled "Determination of Nicotine Dose

12:43:38 Delivered During Human Smoking." I ask you to take a moment to look at it. Take a moment to look at that.

MS. FORBES: For the record, Mr. Sobol,
12:43:46 would you please state how you came into possession of this document.

MR. SOBOL: No.

MS. FORBES: This document was not produced to you, was it, through document --

12:43:56 MR. SOBOL: Ms. Forbes, I'm not the one being deposed today.

MS. FORBES: You can make your record. Go ahead. So you are refusing to state for the record
12:44:06 where you got this document that says "redacted material" on it?

MR. SOBOL: This is in the public domain.

MS. FORBES: Well, we have a disagreement about that. Let's go head and take our lunch break now.

12:44:18 MR. SOBOL: I have a document in front of the witness, I just put in front of him, and you are not letting me ask a question about it before we take a break?

MS. FORBES: You are not telling me where

12:44:24 you got this document? Is it your testimony that -- come on, where did you get this document? It's marked "redacted material." It was not produced to you through ordinary document production in
12:44:36 California, correct, because you have not made such request, correct?

MR. SOBOL: Marilyn, I'm not the one being deposed here.

MS. FORBES: I understand.

12:45:02 (Witness reviews document)

BY MR. SOBOL:

Q. Have you had a chance to review the document, sir, or are you still reviewing it?

12:45:10 A. I'm still reading it.

Q. Okay. Just me know when you have had a chance to fully review it.

MS. FORBES: Continuing for the record, this document, which not produced to Mr. Sobol in
12:45:22 the course of litigation and which he is not willing to state where he got the document, does state "redacted material." For the record, without me knowing more, I would object to the use of this document in this litigation.

12:45:52 MR. KEHOE: Let me go on the record.
Because of the position taken by Ms. Forbes on
behalf of the Defendant, as a former employee of the
Defendant, I'm going to direct Dr. Hayes not to
12:46:04 answer any questions with regard to this document
until the issue of the document is clarified because
it may place him in jeopardy vis-a-vis his former
employer.

MS. FORBES: Mr. Sobol, I'm not trying to
12:46:18 be difficult about this. I would be glad during the
lunch break to check, but when I see this document
that has "redacted material" and you are refusing to
state where you got it, I'm going to check on the
document because I'm not going to risk any kind of
12:46:34 privilege waiver by this examination. I would be
glad to check at lunch.

MR. SOBOL: Let me first direct my comments
to Mr. Kehoe. Mr. Kehoe, this is a deposition
pursuant to California rules of civil procedure, not
12:46:48 Massachusetts Rules of Civil Procedure, and I'm
going to ask you, sir, to tell me what the basis is
that you are instructing this witness not to
answer.

MR. KEHOE: The basis is that he may, by

12:47:02 either jeopardizing the waiver of their claim of privilege, put himself in a position where he is liable to his former employer, and I do not want him to get into a position of liability. So you may get
12:47:20 an order on it if you wish, but I will direct him not to answer.

MS. FORBES: Mr. Sobol, if you would just give me a chance to review this document, determine what this "redacted material" stamp on the left is
12:47:32 over lunch, maybe we can address it appropriately after the break.

MR. SOBOL: I will say for the record there's been no assertion of privilege yet.

MS. FORBES: I'm sorry. I did say that
12:47:44 until I determine that this is not a privileged document based on this "redacted material" stamp -- maybe I wasn't clear -- that I am not going to risk any kind of waiver of the privilege that R.J. Reynolds may have in this document. I would like to
12:48:00 check on it during lunch, and then we will pick up where it's appropriate. But what I specifically don't want to do is risk a waiver of any kind of privilege. That's all.

MR. SOBOL: Let me ask a couple of

12:48:10 questions of the witness, and I don't think they will pertain to privileged matter or any possible assertion of privilege.

MS. FORBES: All right.

12:48:18 MR. SOBOL: I do state for the record that there is nothing on the face of this document which could possibly under any conception of privilege be privileged.

MS. FORBES: Well, I haven't read the

12:48:30 document, but there is a stamp which says "redacted material."

MR. SOBOL: I'm not saying the privilege may have been abused or not. That could very well be. There is nothing on this document that could

12:48:40 conceivably be privileged.

MS. FORBES: Well, if you will stipulate, Mr. Sobol, that the questions you were about to ask Dr. Hayes will not constitute any kind of or be used as any kind of basis of a waiver, then I will allow

12:48:58 you to ask the questions. That's all I want to ensure. And give me a chance in the next ten minutes to check on this document, which you are refusing to state where it came from. This doesn't have to be extraordinarily difficult. Are you

12:49:12 willing to so stipulate?

MR. SOBOL: Let me -- I'm going to ask the witness a couple of questions, and if you want to instruct him not to answer, you may.

12:49:20 MS. FORBES: Are you willing to stipulate that any responses he gives will not be used by you as a waiver or a basis of an argument of a waiver privilege? That's all I'm asking for.

MR. SOBOL: No, I'm not ready to stipulate 12:49:34 to that.

MS. FORBES: Well, then --

MR. SOBOL: Let me ask my questions.

BY MR. SOBOL:

Q. Have you seen this document before?

12:49:40 MR. KEHOE: Don't answer that question.

MR. SOBOL: You are instructing him not to answer whether or not he has seen it?

MR. KEHOE: Yes.

BY MR. SOBOL:

12:49:48 Q. Did you assist in preparing this document?

MR. KEHOE: Don't answer that question.

MR. SOBOL: Okay. Let's take our lunch break.

THE VIDEOGRAPHER: Off the record at 12:49.

(Luncheon recess taken)

AFTERNOON SESSION

THE VIDEOGRAPHER: Back on the record at 2:17.

14:17:24 MS. FORBES: And, Mr. Sobol, as I indicated to you before lunch, I would check on this document during lunch. I did, there's not a privilege claim on this document, and grounds has no objection to the examination based on Hayes No. 1.

14:17:38 MR. KEHOE: Before you commence to reexamine, Mr. Sobol -- I don't want to throw you off your stride -- he has a minor change to his earlier testimony in keeping with his ongoing obligation to straighten out testimony. He would be 14:18:00 inclined to do it now, but you can examine first now.

MR. SOBOL: All right. I will ask him.

BY MR. SOBOL:

14:18:04 Q. During the break, Dr. Hayes, you had an occasion to reflect upon your testimony this morning?

A. (Witness nods head)

Q. Would you answer audibly, please, for the court reporter.

14:18:08 A. Yes.
Q. There's something about your testimony you would like to change at this point?
A. Yes.
14:18:14 Q. What is that?
A. I had forgotten that Sharon Johe from Reynolds called me about John Kehoe, and I went down and visited with him before he became the attorney to represent me. And I had forgotten about Sharon
14:18:34 Johe calling me.
Q. Can you spell her last name, please.
A. J-o-h-e, I think.
Q. And who is she?
A. She is an attorney with R.J.R.
14:18:46 Q. Do you know if she is an in-house attorney?
A. I believe she is.
Q. Had you known her during your time at R.J.R.?
A. Yes.
14:19:00 Q. Did she contact you in regards to this deposition as well?
A. No.
Q. She just introduced you to Mr. Kehoe?
A. Yes.

14:19:08 MS. FORBES: Objection to the form.
Q. Had you heard of Mr. Kehoe before?
A. No.
Q. Had you heard of Mr. Kehoe before Ms. Johe?
14:19:20 A. No.
Q. Sir, you have in front of you, sir, Document No. 1 still. Did you have that with you over the break?
A. No.
14:19:34 Q. Have you seen this document before, sir?
A. I think so.
Q. When did you first see this document?
A. Timewise I don't remember, but I'm sure that I saw it after it was prepared by the people
14:19:52 that prepared it.
Q. Who prepared it, if you know?
A. I do not know for certain. I would guess that John Robinson prepared it.
Q. What is the basis for your testimony that
14:20:14 you believe John Robinson prepared Exhibit No. 1?
A. He is the first author.
Q. He is the first person listed there?
A. That's correct.
Q. And was it customary at R.J.R. to list

14:20:26 first those authors primarily responsible for the document?

A. That is correct throughout the scientific community.

14:20:38 Q. Was John Robinson working for you?

A. He worked in the Biobehavioral Biopharmacology -- or the Biobehavior Biochemical Group.

Q. At the time that you were in charge of that 14:20:46 group?

A. That's correct.

Q. What was his position?

A. He was a scientist. What his title was beyond that, I don't remember.

14:21:04 Q. What was his area of concentration? What kind of work did he do?

A. He was a behavioral psychologist if my memory serves me correctly.

Q. Was Dr. Robinson part of the Biochemical 14:21:30 Biobehavioral Group from 1984 through 1992, the period of time that you were at R.J.R.?

A. Yes.

Q. And you supervised him the entire time?

A. No.

14:21:40 Q. Did he report to you the entire time?
A. No.
Q. When during that eight or so years did he report to you?
14:21:52 A. He never reported to me.
Q. Were you ever his supervisor?
A. No.
Q. You were in charge, sir, of the Biochemical Biobehavioral Group?
14:22:08 A. Yes.
Q. Who in the Biochemical Biobehavioral Group reported to you about Dr. Robinson's work?
MS. FORBES: Objection. Vague.
A. If you mean to whom did Dr. Robinson report, it was Dr. Reynolds.
14:22:26 Q. John Reynolds?
A. Correct.
Q. Did Dr. Reynolds report to you?
A. Yes.
14:22:38 Q. Did Dr. Reynolds report to you about Dr. Robinson's work?
A. On a periodic basis he would update me.
Q. Are you generally aware during the eight years you were at R.J.R. of the work done by John

14:22:56 Robinson within the Biochemical Biobehavioral Group?
A. In a general sense, yes.
Q. Was there anyone other than Dr. Reynolds who would provide you with periodic updates about
14:23:08 Dr. Robinson's work?
A. Not to my recollection.
Q. You certainly knew Dr. Robinson?
A. Yes.
Q. And you had occasion to talk with him about
14:23:20 his work directly from time to time?
A. From time to time.
Q. His name is listed first on Exhibit 1, so you -- is that correct?
A. That is correct.
14:23:36 Q. What's the next name?
A. J.D. DeBethizy.
Q. That's Dr. Don DeBethizy?
A. That's correct.
Q. Did he report directly to you at any time?
14:24:02 A. I don't believe so.
Q. What kind of work did he do within the Biochemical Biobehavioral Group?
A. Pharmacokinetic.
Q. Was that the extent of his work in that

14:24:16 group?

A. To the best of my recollection.

Q. And Dr. DeBethizy developed a pharmacokinetic modeling of nicotine; is that right?

14:24:38 A. I think that's incorrect.

Q. What is incorrect about that, the fact that I called it a modeling?

A. No, the fact that you called it a pharmacokinetic model.

14:24:54 Q. What is it that Dr. DeBethizy did regarding nicotine while he was part of the Biobehavioral Biochemical Group?

MS. FORBES: Objection. Overbroad, vague.

A. He did a variety of things.

14:25:10 Q. Did he do a metabolic modeling of nicotine?

A. Yes.

Q. Would you describe that work for me, please.

A. The details of it again are published.

14:25:24 It's called A Physiologically Based Pharmacokinetic Model, and basically it's a mathematical model that allows you to model metabolic profiles of any number of chemicals. And he was able over the course of time to develop one of these for nicotine. I'm not

14:25:50 sure that he ever completed it, but what he did do has been published, or at least during my tenure everything that he did was published.

Q. Other than developing this physiological
14:26:08 pharmacological model of nicotine, did he do any other similar work regarding other chemicals or substances?

A. I don't remember.

Q. You remember the nicotine?

14:26:16 A. Yes.

Q. And the next name which appears on the Document No. 1 there is, sir?

A. After Dr. DeBethizy?

Q. Yes.

14:26:30 A. R.A. Davis.

Q. Who is R.A. Davis?

A. He was an analytical chemist that was in the Biobehavioral Group.

Q. Who did he report to?

14:26:46 A. To Dr. Reynolds.

Q. Is he a doctor, a Ph.D.?

A. No.

Q. D.W. Griffith, that's the next name?

A. Yes.

14:27:00 Q. Who's that?
A. He was also in that same group.
Q. In the Biobehavioral Group?
A. Correct.
14:27:12 Q. The Biochemical Biobehavioral Group that you ran, sir, did it have subgroups within there?
A. Yes.
Q. What were they?
A. Biobehavioral, toxicology, scientific and
14:27:30 regulatory affairs.
Q. And was D.W. Griffith an analytical chemist as well within Biobehavioral?
A. No.
Q. What was he?
14:27:58 A. I don't remember what his training was.
Q. Do you remember what kind of work he did?
A. He worked with John Reynolds and Riley Davis, and he was involved in some of the machinery that was used by the other folks.
14:28:26 Q. What kind of machinery was that?
A. I think there's one, a programmable smoking machine. He was involved in the development of that particular apparatus.
Q. Is that the one referred to in

14:28:52 Exhibit No. 1?

A. That is correct.

Q. Within the three subgroups of your Biochemical Biobehavioral Group, were there further

14:29:18 subgroups? Maybe it would be easier if we did them one at a time. Were there any subgroups under Biobehavioral?

A. I don't believe so.

Q. Was there a group studying environmental

14:29:32 tobacco smoke within the Biochemical Biobehavioral Group?

A. At one time, yes.

Q. When was that?

A. Toward the end of my time there.

14:29:54 Q. Was it in existence for a matter of years while you were still at R.J.R. or a matter of months?

A. Could you repeat that, please.

Q. Approximately how long was there an

14:30:06 environmental tobacco smoke group within the Biochemical Biobehavioral Group?

A. A couple of years.

Q. Were there any other groups under the Biochemical Biobehavioral Group that you can recall

14:30:30 that you haven't testified to yet today?
A. At one time the industrial hygiene people reported to me.
Q. What is industrial hygiene?
14:30:58 A. The people that do the monitoring and the evaluation for worker safety within the plant itself. I think that's it.
Q. Okay. And J.H. Reynolds is listed after D.W. Griffith, and you said that he was also in the
14:31:38 Biochemical Biobehavioral Group?
A. Correct.
Q. What was the nature of his work?
A. He was a -- he is, was the manager of that Biobehavioral Group.
14:31:58 Q. And that's your name listed last; is that correct?
A. Correct.
Q. Did you participate in the preparation of a document entitled "Determination of Nicotine Dose
14:32:12 Delivered During Human Smoking"?
A. Not in the initial preparation.
Q. What was your role in it?
A. Specifically I do not remember, but in anything that had my name on it, I had read it for

14:32:36 scientific merit to be sure that it was of the caliber that would be representative of the type of work that we did.

Q. This Document No. 1 that is before you

14:32:56 appears to be an abstract of a larger document?

A. If I had to guess, and I'm only guessing, that it's nothing but an abstract.

Q. That Exhibit No. 1 is nothing but an abstract?

14:33:08 A. If I had to guess.

Q. Do you recall, sir, whether or not there is a larger piece of work that goes with this abstract?

A. There is a larger piece, and it's published in that yellow book on Premier, and I would also

14:33:28 guess that it's been published in some scientific peer review journal, but I don't remember which one.

Q. Do you know why it is that the biobehavioral division of your group was studying

14:33:56 methods to determine the nicotine dose delivered during human smoking?

A. For the same reason that they were studying the amount of tar that was delivered during human smoking.

Q. What reason is that?

14:34:10 A. The entire Premier project was a comparative toxicology study in which the Premier cigarette was compared against a standard Kentucky reference cigarette to show if the chemicals in the 14:34:40 Premier cigarette had indeed been reduced, as was the initial mission of that project, to reduce the smoke and thereby reducing the chemicals.

Q. Were they seeking to reduce nicotine?

MS. FORBES: Objection. Vague.

14:34:56 A. I don't think that we ever tried to reduce nicotine.

Q. And nicotine, of course, is a compound in cigarette smoke?

A. That's correct.

14:35:08 Q. So you were attempting to reduce the compounds in cigarette smoke delivered to the human smoker with the exception of nicotine?

MS. FORBES: Objection. Misstates, mischaracterizes.

14:35:18 A. No, I don't think that that was the intent. The intent was to reduce those chemicals in cigarette smoke that had been suggested by a variety of studies, including epidemiology studies, to be involved in adverse effects.

14:35:52 Q. What do you mean by "adverse effects"?
A. Untoward effects.
Q. Effects upon what?
A. Biological systems.
14:36:02 Q. Including human beings?
A. To the best of my knowledge, we never looked at those kinds of in-points in human beings.
(Mr. Maistros leaves the deposition room)
Q. The goal of the Premier project ultimately, sir, was to put a cigarette out on the market, is that correct?
14:36:44 A. That's correct.
Q. Who was going to smoke that cigarette?
MS. FORBES: Objection. Vague.
14:36:52 A. I suppose the same people that would smoke any other cigarettes.
Q. They would be people?
A. That's correct.
Q. And the idea was to reduce those compounds, those chemicals and cigarette smoke that had been
14:37:04 suggested to be involved in adverse health effects so that people could smoke a cigarette without those compounds; is that right?
MS. FORBES: Objection. Vague.

14:37:18 A. The first two-thirds of that statement are what I said. You had it the latter part.

Q. Well, I'm asking you if that is the case.

A. And what I said was it was to reduce those 14:37:32 chemicals that were in smoke that had been suggested to have adverse effects.

Q. Suggested to have adverse effect, and you say --

A. In humans.

14:38:02 Q. In humans. Okay. The notion of producing a cigarette with less smoke, is that a euphemism, sir, for producing a cigarette that is less likely to cause cancer in human beings?

MS. FORBES: Objection. Argumentative.

14:38:18 A. In my opinion, if you can reduce those chemicals that are suggested to cause an adverse, untoward effect, then you eliminate that adverse or untoward effect.

(Mr. Maistros enters the deposition room)

14:38:38 Q. My question, though, is whether or not the phrase "producing a cigarette with less smoke" is a euphemism for producing a cigarette that is less likely to cause cancer.

MS. FORBES: Objection. Argumentative,

14:38:50 vague, asked and answered.

A. I don't think that I can answer that question, because I know of no example save one or two in which -- actually, I don't know of any -- in

14:39:06 which cigarette smoke has caused lung cancer in experimental animals.

Q. By that you are referring to inhalation studies; is that correct?

A. That's correct.

14:39:16 Q. Because you are familiar with the smoke condensate studies that have produced tumors; is that correct?

A. Skin painting studies; that's correct.

Q. In fact, didn't part of the Premier

14:39:28 investigation involve skin painting?

A. That's correct.

Q. But the goal of producing a Premier cigarette and putting it out on the market wasn't to have less tumors on mice back; isn't that correct?

14:39:40 MS. FORBES: Objection. Argumentative.

A. My goal was to reduce those chemicals full stop.

Q. I'm wondering, sir, if you can read the first sentence of this abstract marked as

14:40:22 Exhibit No. 1 into the record. Out loud.
A. Oh, okay. "The 'tar' and nicotine values that are determined by the Federal Trade Commission (F.T.C.) machine smoking method do not always
14:40:40 reflect the amount of NIC delivered to or absorbed by an individual smoker."
Q. Now, that's a statement which you read to determine its scientific merit; isn't that correct?
A. That's correct.
14:40:52 Q. And back at the time that you reviewed this document, did you believe that statement to have scientific merit?
A. Yes.
Q. Do you still?
14:40:58 A. Yes.
Q. Do you know what efforts R.J. Reynolds has made to inform its smoking consumers that the tar and nicotine values that are determined from the F.T.C. method do not always reflect the amount of
14:41:16 nicotine delivered or absorbed in a human smoker?
MS. FORBES: Objection. Vague.
A. The only thing that I know is what I have done.
Q. So you know of no such efforts; is that

correct?

MS. FORBES: Objection. Misstates and mischaracterizes.

Q. What efforts have you taken on your behalf personally, sir, to inform the smoking public that the tar and nicotine values determined by the F.T.C. smoking method do not accurately reflect the nicotine delivered or absorbed by an individual smoker?

14:41:34
14:41:46

MS. FORBES: Objection to the extent that that is not what this document states.

MR. SOBOL: The question stands alone.

14:42:00

A. All this document says is that the F.T.C. smoking machine does not reflect what the human smoker gets. From the beginning of the time that the F.T.C. methodology was developed, it always stated it's a comparison between cigarettes. To the best of my knowledge, it never said that this is how much or how little a smoker gets. It's only

14:42:22

reflective of how much is yielded by that cigarette under those very specific conditions of the F.T.C. methodology.

Q. Okay, sir. Is it your position that the F.T.C. smoking method would accurately reflect the

14:42:40 comparisons of different cigarettes?

A. It would accurately reflect the yield of tar and nicotine of different cigarettes as smoked on that F.T.C. machine.

14:42:56 Q. And would the effect of ventilation, sir, disproportionately skew an F.T.C. yield as compared to that absorbed by the human smoker?

MS. FORBES: Objection. Vague.

A. Would it obscure?

14:43:12 Q. That wasn't my statement, no. Let me rephrase the question for you, sir.

A. Okay.

Q. I'm asking you whether or not the F.T.C. smoking method would provide an accurate relative comparison among all cigarettes.

14:43:28 MS. FORBES: Objection. Vague.

A. To the best of my knowledge and recollection, it should give a fair, comparable reflection if the methodology is used appropriately.

14:43:56 Q. Now, the --

MS. FORBES: Why don't we just hold off.

(Telephone interruption)

(Mr. Holton leaves the deposition room)

Q. The F.T.C. smoking method would give you

14:44:30 one amount for -- excuse me. The F.T.C. smoking method would give you one set of values, say, for the Premier prototype; is that correct?

A. I'm not sure I understand that question.

14:44:42 Q. You have the F.T.C. smoking machine. You say you run the Premier through it, you get a set of values, and then you have another method which shows a different value of, say, nicotine was delivered to the smoker; is that right?

14:44:54 MS. FORBES: Objection. Vague.

A. What is the other method that we talked about?

Q. I don't know. Did you use more than one method with the Premier cigarette other than the F.T.C. method?

14:45:00 A. We used the F.T.C. method and the method that's reported here.

Q. What is the name of that other method that is reported here?

14:45:14 A. "Programmable smoking machine."

Q. So if you ran the Premier cigarette through the F.T.C. smoking method, you would get one value, and you get a different value, is that correct, if you ran it through the programmable smoking machine?

14:45:32 A. They are measuring two entirely different things, and so because they are measuring two entirely different things, you would get a different value.

14:45:44 Q. And if you compared those two values, would they be in a relationship that would be consistent among all kinds of cigarettes, sir?

MS. FORBES: Objection. Vague and ambiguous.

14:45:56 Q. Do you understand my question?

A. Not really.

Q. Okay. You have two different values, and I'm asking you whether or not the relationship between those two values is constant over all kinds of cigarettes.

14:46:08 MS. FORBES: Objection. Vague and ambiguous.

A. I don't know the answer to that question.

(Mr. Holton enters the deposition room)

14:46:38 Q. Is it possible, sir, to determine from the F.T.C. smoking method value what the value would be for the programmable smoking machine?

MS. FORBES: Objection. Vague and ambiguous.

14:46:52 A. I don't know if that comparison has ever been made. If it has, I don't remember seeing it.

Q. Okay. You state here that R.J.R. has "integrated a series of research techniques that

14:47:22 enable us to determine nicotine delivered during human smoking and to apply these techniques to the study of nicotine pharmacokinetics." How was that application, how was that done?

A. Again I would refer you to that yellow book

14:47:38 and to the published peer review literature. My recollection is very hazy, but there would be some metabolite that would be evaluated in either the blood or the urine to work out the area under the curve. But the details, I don't remember. But

14:48:08 again, they are published in the yellow book on Premier and in the open literature.

Q. And how is it that puff parameters, including volume, duration, rate, shape, number and intensity, would relate to the metabolism of

14:48:30 nicotine by the human smoker?

A. Only in light of the fact that one measures the amount of smoke that goes into the smoker and the other measures specific metabolites. Beyond that, again my recollection is fuzzy, and I would

14:48:56 refer you to those documents that I have stated earlier.

Q. Do you know whether or not the programmable smoking machine developed by R.J.R. could account or

14:49:12 accommodate differences in draw of a cigarette?

A. I don't remember.

Q. Do you know, are you familiar with the concept of "draw" as it relates to cigarettes?

A. The term I remember. The details I don't remember.

Q. Have you ever heard the term "pressure drop" as it relates to cigarettes?

A. I'm sure I have, but again I don't remember

14:49:40 the details.

Q. Do you have an understanding of how draw may relate to nicotine yield to the smoker?

A. No.

Q. Do you know how pressure drop may relate to the nicotine yield of the smoker?

14:49:52 A. No.

Q. Do you know how it is that the development of a programmable smoking machine was essential to the determination of the pharmacokinetic properties of nicotine derived from cigarette smoking?

14:50:08 MS. FORBES: Objection. Vague.
A. How it was essential, no.
Q. Okay. Referring you to the last sentence
of this document, can you read that into the
14:50:20 record.
A. "These techniques are essential to the
determination of the pharmacokinetic properties of
nicotine derived from cigarette smoking."
Q. Do you know how that was so, sir?
14:50:36 A. I don't remember.
Q. Is it your -- do you have a memory as to
whether or not the programmable smoking machine
could be programmed for taking into account these
different puff parameters referred to in the
14:51:06 document?
A. As I remember, yes, it could be.
Q. Do you know whether or not the programmable
smoking machine was used outside the context of
Premier?
14:51:28 MS. FORBES: Objection. Vague.
Q. Let me rephrase the question. Do you know
whether or not the programmable smoking machine was
used other than on Premier cigarettes or Kentucky
reference cigarettes?

14:51:44 A. My recollection is that it was, but I don't know the details.

Q. Do you know whether or not the biobehavioral group employed the programmable

14:51:52 smoking machine with regard to R.J.R. brand cigarettes?

A. Again my recollection says possibility, but I don't recall.

Q. Outside of the work on Premier, do you

14:52:30 recall any use of the programmable smoking machine specifically?

A. No specific recollections, no.

Q. Do you know how many of these machines R.J.R. had at the time you left in 1992?

14:52:40 A. No.

Q. Do you know if they had more than one?

A. My recollection says that it was more than one, but I don't know.

Q. I'm going to mark, sir, Exhibit No. 2, and

14:53:28 it's a lengthy document. I'm only going to ask you about certain parts of it. You are certainly free to review the entirety of the document if you wish. I nonetheless will direct you to certain parts of it for my question, but I want you to understand that

14:53:46 you have an opportunity to review whatever part of this document is necessary for an accurate and honest answer. Do you understand that?

A. Yes.

(Document marked as Hayes Exhibit 2 for identification)

(Witness reviews document)

Q. For the record, I'll state that the photocopy of this document seems to have been
14:54:46 misstapled, certain parts of it, which I apologize for. And my paralegal has also put in an extraneous page which you are welcome to keep.

(Discussion off the record)

MS. FORBES: Also missing a page at least.
14:55:54 It appears that 9204 is not here, which is where we had the -- maybe the Bates No. 9204 is missing from the document.

MR. SOBOL: Okay. Well --

MS. FORBES: So wherever an inadvertent
14:56:14 page was placed, we missed the actual page, so it's not a complete document.

Q. You have had a chance to briefly familiarize yourself with this document?

A. Briefly.

14:56:28 Q. Do you recognize it?
A. No.
Q. Do you recall at any period of time which you were heading the Biochemical Biobehavioral Group
14:56:46 where you had Dr. Reynolds give you status reports regarding the biobehavioral research division?
A. Yes.
Q. And does this document appear to be one of those status reports to you?
14:56:58 A. It says it is a status report, fourth quarter 1985, January 16, 1986.
Q. Is the date of the document?
A. That's correct, and it's for the fourth quarter of the prior year.
14:57:18 Q. I want to direct your attention to the second page of the document.
A. 9202?
Q. 9201. Do you recall the Biobehavioral Division's objective to "develop an improved means
14:57:38 to accurately determine doses of smoke components to smokers and relationships of smoking behavior patterns to product properties"?
A. Are you reading someplace?
Q. I am reading "Plan Objective 1." Do you

14:57:48 recall that "Plan Objective 1" in the Biobehavioral Division?

A. No, but as I said earlier, it probably was done.

14:57:58 Q. Do you see the reference under sub (a) to the human-mimic smoking machine?

A. Correct.

Q. Is that the programmable smoking machine you referred to earlier?

14:58:08 A. Correct.

Q. Are you familiar with the abbreviation HMSM for "human mimic smoking machine"?

A. Yes. First sentence of (a) indicates that that is what it is, yes.

14:58:32 Q. Do you know, do you have an understanding independent of this document, sir, what the massage of puff profile data would be?

MS. FORBES: Well, objection to the extent the sentence refers to the software, but...

14:58:54 A. The most recent version of software. And not being a programmer, I wouldn't know what they have done within that program.

Q. Okay. Let me refer you a little bit further down in the document. There's a sentence

14:59:12 that begins, "At this time selected, single puffs can be 'massaged,' but if testing confirms expectations of performance, extension to multipuff replication will be relatively easy." Do you know
14:59:22 what they mean by single puffs being massaged?

A. At this time, single puffs can be massaged, but if testing confirms expectation of performance... I don't recall.

Q. Do you recall discussing with Dr. Reynolds
14:59:58 the concept of massaging the puff profile?

MS. FORBES: Objection. Misstates and mischaracterizes.

A. Again I don't recall getting into that kind of detail with him, no.

15:00:22 Q. Okay. I want to refer you down a couple of paragraphs where it says, "The continuing analyses of these data have focused on two major areas. First, the exploration of the dependency of plasma nicotine concentrations on puffing and/or breathing
15:00:36 behaviors, and second, the examination of the "after-puff" breaths to determine how they relate to either the smoker or the cigarette smoked."

Do you see that?

A. Yes.

15:00:52 Q. Do you recall the Biobehavioral Division performing analyses which focused on those two areas?

A. No.

15:01:00 Q. Do you know whether or not the Biobehavioral Division ever published regarding those two areas?

A. No.

Q. If the Biobehavioral Division had published
15:01:12 regarding those two areas, would you have reviewed that material before releasing it for publication?

MS. FORBES: Objection.

A. Yes.

Q. Do you know why the Biobehavioral Division
15:01:30 was investigating the dependency of plasma nicotine concentrations on puffing and/or breathing behaviors?

A. No.

Q. Do you know what "after-pull breaths" mean?

15:01:46 A. No.

Q. And therefore you wouldn't know why it is that the Biobehavioral Group was examining the after-puff breaths to determine how they relate to either the smoker or the cigarette smoked?

15:01:58 A. I don't recall, no.

Q. The next sentence says that there was a report in the previous quarter regarding changes in nicotine concentrations in the plasma of smokers.

15:02:16 Do you see that?

A. "Were similar whether the cigarette smoked was Winston or Marlboro."

Q. Do you remember that study comparing Winston or Marlboro?

15:02:26 A. No.

Q. Do you recall the Biobehavioral Division concluding that "although individuals are different from one another in puffing behavior and in plasma nicotine concentrations attained, the cigarettes

15:02:50 smoked do not appear to be associated with consistent significant differences in these variables"?

MS. FORBES: Objection. Lack of foundation.

15:02:56 A. I don't see where you are reading.

Q. It's a few sentences down.

MS. FORBES: Do you want to identify it for him.

A. "Although the puff profile data from this

15:03:06 experiment"; is that the sentence?

Q. No, the next sentence, sir.

A. "That is, although individuals are different from one another in puffing behavior and

15:03:20 in plasma..." Yes, I see the sentence.

Q. Do you recall that work being done?

A. No.

Q. Do you recall Biobehavioral Division reaching that conclusion in the fourth quarter of

15:03:28 1985?

A. No.

(Document marked as Hayes Exhibit 3 for identification)

Q. Exhibit No. 3, sir, is a weekly highlights

15:04:26 of the Biochemical Biobehavioral Division written to you from Dr. Di Marco.

(Witness reviews document)

Q. Have you had a chance to review the document, sir?

15:06:50 A. Yes.

Q. Do you recognize this one?

A. Specifically, no, but I remember the highlights.

Q. Directing your attention to the third page,

15:07:04 does that appear to be a copy of your signature?

A. That may not be my signature.

Q. Who was your secretary?

A. Jill P. -- no, wait a minute.

15:07:22 Q. You might want to look on the last underneath your name page off to the left there.

A. Brenda. I can't remember her last name.

Q. Had you from time to time authorized Brenda to sign your name?

15:07:34 A. Yes.

Q. And if that is not a copy of your signature, would it be your belief, sir, that you had directed Brenda to sign this document on your behalf?

15:07:46 A. I would almost guess that's not my signature.

Q. Does this document appear to you to be an accurate memo that you sent to Dr. Di Marco on or about August 7, 1984?

15:08:02 A. I couldn't verify it, but it looks reasonable.

Q. Do you have any reason to believe that it's not?

A. No.

15:08:16 Q. Now, I direct you to Page 1. The first thing stated on the document is "Items of general interest to R&D." Would it be correct, sir, that the items listed under "General Interest to R&D" 15:08:32 extended beyond work done with Premier?

MS. FORBES: Objection. Vague.

A. Yes.

Q. On the first page still, the nicotine pharmacology research that was conducted as part of 15:08:56 the Biobehavioral Group, was that work entirely related to -- I'm sorry. Was that work related to Premier?

MS. FORBES: Objection. Vague.

A. If my memory serves me correctly, this is 15:09:12 the work, both A and B, that was published in a book on nicotine by Raven Press, and I think that this is just broad general pharmacology that was carried out by individuals on a grant basis at a medical school, both at Bowman Gray and at the University of Texas.

15:09:42 Q. Do you recall the title of that book?

A. Nicotine Pharmacology. It's a purple book about that thick (indicating), and it's edited by at least Deadwyler and a couple of other folks. It's a Raven Press book. I brought it last time. Your

15:10:00 colleague has it somewhere or had access to it.

Q. Did you review R.J.R.'s submissions to that publication?

A. R.J.R.'s submissions, yes.

15:10:20 Q. Why was R.J.R. studying the electrophysiology of nicotine?

A. My recollection is that it was a proposal that was submitted by the Bowman Gray people, and it looked like it was good, sound science that might further the understanding of the brain, so we funded it.

15:10:46 Q. Other than the fact that it looked to you to be good scientific study, was there any other reason why R.J.R. would be interested in the

15:11:04 electrophysiology of nicotine of which you were aware?

A. I don't remember.

Q. Do you know whether or not the folks at Bowman Gray ever provided R.J.R. with written

15:11:32 results of their study of electrophysiology of nicotine?

A. Certainly as reprints from the peer review public literature. I don't remember if they supplied it in any other format.

15:11:50

MR. SOBOL: We have to change the tape. Maybe it's a good time for a break.

THE VIDEOGRAPHER: Going off the record. This is the end of Tape No. 1. The time is 3:11.

(Recess taken)

THE VIDEOGRAPHER: We're going back on the record. This is Videotape No. 2 in the deposition of A.W. Hayes. The time is 3:20.

(Mr. Holton is present)

BY MR. SOBOL:

Q. Dr. Hayes, you are still under oath. You understand that?

A. Yes.

15:28:26

Q. Do you still have in front of you Exhibit No. 3?

A. Yes.

Q. Do you recall whether or not R.J.R. funded the research of the electrophysiology of any other smoke compound, cigarette smoke compound than

15:28:44

nicotine?

A. I don't, no.

MS. FORBES: I'm sorry. Could I have the last question back again.

(*Question read)

15:29:10 MS. FORBES: Thank you.

Q. Do you have an understanding of why it is that the electrophysiology of nicotine, as opposed to other smoke compounds, was of interest?

15:29:28 A. I don't know. You would have to ask Dr. Deadwyler why he chose that particular compound in his proposal.

Q. There's nothing about the physiological effects of nicotine which makes it a candidate for

15:29:46 studying its electrophysiology?

MS. FORBES: Objection. Vague and ambiguous.

A. I don't know the answer to that.

Q. Do you recall any conclusions reached by

15:29:58 virtue of the study of electrophysiology of nicotine referred to in Exhibit No. 3?

A. No, but as I have stated earlier, they had been published in the peer literature, both as single publications and in that book on nicotine

15:30:16 pharmacology published by Raven Press.

Q. And you would have reviewed those publications prior to it being published?

A. The R.J.R. ones, not the Deadwyler or the non-R.J.R. ones.

15:30:30 Q. So this work funded by R.J.R. would not be the kind of work you would have reviewed prior to publication?

MS. FORBES: Objection. Argumentative.

15:30:36 A. That's correct.

Q. Okay. I'm referring you to Page 2 under "Physiology of Smoking." It refers to a pilot study of the effects of heart rates of smoker during social conversations. Do you recall that work?

15:30:56 A. Very, very vaguely.

Q. What is a pilot study?

A. It's what one might call a feasibility study. Do you have the technology, the capability of carrying out the study as you designed it using small numbers, and if you can carry out the study as

15:31:20 designed, then you would carry it into a full-blown study with more experimental subjects.

Q. Do you recall why there was an interest in determining the effects of smoking on heart rates

15:31:34 during social conversations?

A. Vaguely I recollect that there was something in the literature that said that smoking had a calming effect and reduced heart rate, and this was done to verify that.

15:31:52 Q. Do you recall the results of this study?

A. Vaguely that indeed it did slow down the heart rate, but whether it was significant or not, I don't remember.

15:32:32 MS. FORBES: Mr. Sobol, before you leave this document, you have not examined him on a portion of this document in which, from my understanding, a redacted version, but not this version, has been produced in Minnesota; that this

15:32:52 is a version that is still privileged based on Bates Page 4033, and Reynolds continues to assert its privilege in that portion of the document, which involved -- this is a production that was compelled and not done voluntarily. Reynolds maintains its

15:33:16 privilege on that portion of the document under "Scientific Affairs."

MR. SOBOL: Obviously we disagree about whether or not R.J.R. has waived its privilege and whether or not the productions that Representative

15:33:44 Bliley was voluntarily or not.

MS. FORBES: So the record is clear, this is unauthorized use of this document, and it is a compelled disclosure.

BY MR. SOBOL:

15:34:04 Q. Dr. Hayes, do you recall taking a trip to Germany in the fall of 1984?

A. No.

Q. Do you recall going to Germany at all in connection with your work at R.J. Reynolds?

15:34:16 A. Yes.

Q. Did you do it more than once?

A. I believe so.

Q. Do you remember when the first time was?

15:34:24 A. No.

Q. Do you recall the purpose for your going that first time you went to Germany on behalf of R.J.R.?

A. I don't recall the first time I went.

15:34:40 Q. You don't recall anything about it?

MS. FORBES: Objection. Argumentative.

A. No.

Q. Do you recall if you went alone or with somebody?

15:34:50 A. If I don't recall the trip, it would be hard to recall whether I was alone or with somebody.

Q. Do you recall anybody you met and talked with there?

A. I don't recall the trip.

15:35:08 Q. How many times did you go to Germany in connection with your work at Reynolds Tobacco?
A. I don't know.
Q. Was it more than 12?
15:35:18 A. Probably not.
Q. Was it more than three times?
A. I don't know the answer to that.
Q. Is there any specific reason why you can't recall your trips to Germany?
15:35:30 MS. FORBES: Objection. That's argumentative.
MR. KEHOE: Don't answer that question.
A. No.
Q. Have you heard of R.J. Reynolds Tobacco International?
A. Yes.
Q. What is R.J. Reynolds Tobacco International?
A. When I first came to Reynolds, it was the
15:35:54 international arm of the tobacco company.
Q. What was the function of the international arm of the tobacco company?
A. I would assume to sell cigarettes outside of the United States.

15:36:14 Q. Do you know whether or not R.J. Reynolds Tobacco International had a research facility in Germany?

A. Yes.

15:36:22 Q. Did they?

A. Yes.

Q. Where was it?

A. Cologne.

Q. Do you recall whether or not your trips to Germany on behalf of R.J.R. were to Cologne?

15:36:32 A. At least one of them was.

Q. When you went on that trip for R.J. Reynolds to Cologne, did you visit the research laboratory there?

15:36:46 A. Yes.

Q. Do you recall why you were visiting the research laboratory there?

A. Probably for an orientation.

Q. An orientation regarding what?

15:36:58 A. What they did there.

Q. What did they do there?

A. Looked at cigarette blending, cigarette making.

Q. Anything else?

15:37:16 A. Not to my recollection.
Q. Do you recall whether or not they did any research regarding the toxicology of tobacco additives?
15:37:30 A. If they did, I didn't know about it.
Q. Have you ever heard of Oscar Stuhl?
A. Yes.
Q. Have you ever met Oscar Stuhl?
A. Yes.
15:38:04 Q. Where did you meet him first?
A. I don't remember.
Q. Was it in Germany?
A. It could have been.
Q. Did you meet with Mr. Stuhl when you went to Cologne, Germany, and visited the R.J.R. Tobacco
15:38:16 International research laboratory?
A. I'm sure I did.
Q. Do you recall the reason for your meeting with Oscar Stuhl then?
15:38:26 A. No.
Q. Have you ever heard of Bernd Pelz?
A. Yes.
Q. Who is that?
A. I believe he was the director of the

15:38:42 research group in Cologne.

Q. Do you know what the nature of his research was?

A. I'm assuming that since he ran that
15:38:52 operation and it had to do with cigarette making and blending, that's what he did.

Q. Are you aware of the existence of the Scientific Affairs Group within R.J.R. Tobacco International?

15:39:12 A. Vaguely.

Q. What is the Scientific Affairs Group within R.J.R. Tobacco International?

A. I think it was Oscar's. Oscar Stuhl. I think that was it.

15:39:34 Q. That Scientific Affairs was Oscar Stuhl?

A. If my memory serves me correctly, yes.

Q. Do you know what Oscar Stuhl did on behalf of the Scientific Affairs Group within R.J.R. Tobacco International?

15:39:50 A. Details, no. My feeling is that he would have done basically the same thing that any other Scientific Affairs Group would do, and that would be to keep up with the literature of interest to that organization.

15:40:16 Q. Do you recall discussing with -- is it Dr. Stuhl?

A. I don't remember.

Q. Do you recall discussing with Oscar Stuhl
15:40:34 the issue of pesticides getting into tobacco?

A. Not specifically, no.

Q. Do you recall that generally?

A. I would guess that as part of the interest in that arena, that we probably did discuss
15:40:56 pesticides, since tobacco is an agricultural crop.

Q. Do you recall discussing the implications of pesticides making the tobacco smoke toxic?

MS. FORBES: Objection. Vague, lack of foundation.

15:41:14 A. No.

Q. Do you recall discussing with him their research to determine the toxicity of chemicals found in pesticides used on tobacco?

A. His research?

15:41:30 Q. Uh-huh.

A. No.

Q. Do you know whether or not Dr. Suber's work regarding toxicology of the various smoke chemicals was shared with R.J.R. Tobacco International?

15:42:02 MS. FORBES: Objection. Vague, overbroad.
A. Yes.
Q. Was it?
A. Yes. If you look on Page 4033 of
15:42:16 Exhibit 3, you will see a position paper on 11
additives used by R.J.R. McDonald, which was part of
R.J.R. International, were given to Derrick
Crawford, so yes, they were shared. There's an
example.
15:42:32 Q. Who is Derrick Crawford?
A. As I remember, he was the R&D director of
R.J.R. McDonald. McDonald, is that right? Yes,
R.J.R. McDonald, which was a Canadian operation of
the International Group.
15:42:50 Q. Why is it that that information would be
shared with R.J.R. Tobacco International? How would
that assist them in cigarette blending and cigarette
making?
MS. FORBES: Objection. Compound, vague.
15:43:04 A. The same way that it would help the
domestic company.
Q. What way is that?
A. To understand the types of materials that
were being used in the blending process.

15:43:30 Q. Do you know whether or not the research division in Germany was evaluating the chemical compounds in cigarette tobacco smoke against the Ames assay?

15:43:44 A. No.

MS. FORBES: Objection. Vague.

Q. Do you know whether or not at any time R.J.R. Tobacco International performed research regarding health and smoking issues?

15:44:16 MS. FORBES: Objection. Vague.

A. No.

Q. You don't remember that?

A. (Witness shakes head)

15:44:34 Q. Were you aware of a policy at any time, sir, that R.J.R. Tobacco International was not to share any of its health and smoking information with the R&D people in Winston-Salem? Do you remember that?

MS. FORBES: Objection. Vague.

15:44:44 A. No.

Q. Do you remember -- do you have an understanding, sir, if at any time R.J. Reynolds had a policy that materials related to the efforts made on behalf of R.J.R. Tobacco International in studies

15:45:28 related to health wouldn't be shared with -- let me rephrase.

Do you have an understanding, sir, at any time, wasn't there a policy that R.J.R. Tobacco 15:45:38 International was not to share its studies related to health with the R&D department in Winston-Salem?

MS. FORBES: Objection. Vague.

A. Not to my knowledge.

Q. Do you recall discussing passive smoking 15:45:58 with Oscar Stuhl and Bernd Pelz in Cologne?

A. I very well could have, but no, I don't recall anything.

Q. I'm going to mark Exhibit No. 4 -- it's a November 8, 1984, document regarding your trip to 15:46:22 Cologne -- and ask you to take a look at it and see if it refreshes your memory. I have a copy here for everybody, but once again there's a stray piece.

(Document marked as Hayes Exhibit 4 for identification)

15:46:30 A. This is my signature. See the difference?

Q. I believe you. That was too well done for the other one. Take your time to review the documents, sir, but what I will really want to point your attention to is the paragraph which begins at

15:47:14 the very bottom of Page 3.
A. Paragraph bottom of the third page?
MS. FORBES: Mr. Sobol and Dr. Hayes,
before you answer, this memorandum of November 8,
15:47:38 1984, specifically discusses meetings with counsel
for R.J. Reynolds, and this portion of the document
at least is privileged, and Reynolds continues to
assert its privilege concerning any discussions with
lawyers protected by attorney work product and this
15:47:58 privileged and confidential information.
MR. KEHOE: So based on my earlier
objection on -- statement on the record rather --
I'm going to instruct Dr. Hayes not to answer any
questions about this document or at least that
15:48:20 portion of the document that Ms. Forbes has just now
stated her objection to.
MS. FORBES: Mr. Sobol, if you want to
examine from a redacted version where the privileged
materials have been redacted out as they have been
15:48:32 produced, we don't object, but we do object --
MR. SOBOL: Well, look, this witness has
testified as to serious lack of memory regarding his
trip to Cologne and to the policy to withhold
smoking and health research from R.J.R.'s domestic

15:48:54 offices, and this document is his words. And I
would like to see if it refreshes his memory as to
that policy. I'll pull the document from him, but
he has had a chance to review, and I want to further
15:49:06 examine him on the subject matter.

MS. FORBES: I'm not going to change my
position.

MR. MAISTROS: I would request on behalf of
Plaintiffs in New York that as you did with the
15:49:14 other document, you search and determine if this was
among the 39,000 that have been released and are
among those on the Internet available to the public
before you instruct the witness not to answer about
the documents, especially since all those documents
15:49:28 have been released publicly.

MS. FORBES: The fact that they are on the
Internet by a third party has nothing to do with
whether or not the privilege is maintained by the
company. Wrongful acts by third parties can't waive
15:49:42 our privilege. Why don't we go ahead and take a
break, and we'll see if -- do you have the redacted
version?

MR. SOBOL: I'm not aware of any redacted
version.

15:49:52 MS. FORBES: Why don't we go ahead and take
a break. Let's go off the record.

THE VIDEOGRAPHER: Off the record at 3:49.

(Recess taken)

15:59:34 THE VIDEOGRAPHER: Back on the record at
3:59.

MS. FORBES: Reynolds maintains that this
document is wholly privileged and would instruct you
or advise you that this is a wrongfully obtained
15:59:56 document. We do not waive any of our privilege on
this document. And for ease of continuing today,
what I would like to suggest, tomorrow morning I
will have a computer here where I will have that
information about the privileged context of that. I
16:00:16 don't have that here today.

I want to use our time well. To the extent
you want to continue and have questions that are not
related to documents, let's go ahead and go to 5:00
today. If you are not comfortable with that, I
16:00:36 think we either need to suspend or get a ruling from
the judge. But it is my view that probably the hour
could best be used either examining without
documents rather than popping up and down right now,
since I can't tell from what you are presenting me

16:00:52 that what has been redacted and what is privileged.

MR. SOBOL: Well, I resent the implication that this is a wrongfully obtained document. This is a document which has been publicly available are

16:01:02 Worldwide Web. Virtually anybody in any corner of the globe can get a copy of this document if they want to. There is nothing wrong, and there's absolutely no precedent for the position that going on the Internet and downloading a document such as

16:01:16 this, which has been produced to the United States government, is wrongful. I resent the implication.

It is not a privileged document. The production to Congress was completely voluntary, and R.J.R. had at its disposal a number of procedural

16:01:32 safeguards which it could have invoked in order to preserve the privilege. It chose not to because it was seeking to get benefits from Congress in terms of the global settlement. That was a strategic decision that your client made, and I will ask

16:01:48 questions about the document. If you want to instruct him not to answer, you can.

I also, of course, am going to ask him about the subject matter. The subject matter, as far as I know, of whether or not R.J. Reynolds

16:02:08 withheld information from its own research department in order to avoid controversies regarding the health effects of smoking, I don't believe is a subject which you can claim privilege to, nor has
16:02:18 that been done.

MS. FORBES: Well, obviously that's correct, Mr. Sobol. You are entitled to examine on any facts. That is why the witness is here. He is here to tell the truth about the facts you want to
16:02:30 ask him about. But it is absolutely clear that it's Reynolds' position that a compelled disclosure does not equal a waiver, and as you know, Reynolds has won, there is precedent in the State of Washington on this. So your statement is incorrect. Reynolds
16:02:46 has prevailed on this issue in the State of Washington, which is a case you are well aware of, so you and I can agree that we disagree. We won't solve the problem. It's your deposition. You can proceed until 5:00, as you wish. I'm trying to make
16:03:04 good use of time and not be unduly difficult, but --

MR. SOBOL: Let's try a few questions and see if whether or not you feel that information would be privileged.

BY MR. SOBOL:

16:03:14 Q. Sir, is that a copy of your signature on the last page?

MS. FORBES: Objection.

MR. KEHOE: I direct you not to answer.

16:03:26 Q. Sir, does that document refresh your memory as to whether or not there was a directive not to share health research between R.J.R. International and R.J.R. in Winston-Salem?

16:03:36 MS. FORBES: Objection. It's a privileged and confidential document which may not be used to refresh the witness's recollection.

MR. KEHOE: I direct Dr. Hayes not to answer.

MR. SOBOL: Now may I have Exhibit No. 4, 16:03:48 sir. I will just put that over here with the court reporter.

Q. Let me ask you here again, sir, while you are under oath --

MS. FORBES: Excuse me?

16:03:56 MR. SOBOL: I said I want to ask him again while he is under oath.

MS. FORBES: I'm sorry.

Q. -- whether or not you recall that there was an instruction at R.J. Reynolds not to share

16:04:14 health-related research between R.J.R. Tobacco International and R.J.R. Winston-Salem.

MS. FORBES: Objection. That is an abusive and argumentative question. It's obvious when he is

16:04:24 under oath he is under oath throughout the entire deposition. Would you rephrase your question.

MR. SOBOL: No.

MS. FORBES: Same objections. Please don't be abusive to this witness.

16:04:40 MR. KEHOE: You can go ahead and answer that one.

A. Could you repeat the question. I got lost in all of that.

MR. SOBOL: I don't blame you, sir. I

16:04:50 think perhaps the reason for it --

MS. FORBES: Motion to strike.

Q. I'm asking you, sir, whether you recall a policy that R.J.R. Tobacco International was not to share with R.J.R. Tobacco Company in Winston-Salem

16:05:10 its research regarding the health effects of smoking.

MS. FORBES: Objection. Lack of foundation.

MR. KEHOE: You can answer that one,

16:05:16 Dr. Hayes.

A. At the time when I discovered that that had occurred, I took it to my immediate supervisor, Dr. Di Marco, and that was changed immediately.

16:05:30 From thenceforward on, it was shared.

Q. How long had that policy been in effect, if you know, before you brought it to Dr. Di Marco's attention?

A. I don't know. That's...

16:05:52 Q. But it was your understanding that there was such a policy in effect?

A. That's --

MS. FORBES: Objection.

A. -- what I was told.

16:06:00 Q. Who told you that?

A. Based on reading of the Exhibit No. 4, Oscar Stuhl.

MS. FORBES: Same objection now.

MR. SOBOL: You are objecting to his

16:06:14 answer?

MS. FORBES: I am. It's based on privileged document, and I don't want to have any waiver argument based on our failure not to object. I just want to make sure the record is clear.

16:06:26 A. And I'd like to correct. I misstated when I said that I didn't think Oscar had a Ph.D., and according to that, he did have a Ph.D.

MS. FORBES: Same objection.

16:06:44 Q. Subsequent to your discussion with Dr. Di Marco, what health-related research was shared by R.J.R. Tobacco International with R.J.R. domestic?

A. To the best of my recollection, everything that we asked to see was shared.

16:07:06 Q. Is it your testimony now that R.J.R. Tobacco International was engaged in research regarding the health effects of smoking?

A. R.J.R. Tobacco International was not engaged in research related to anything other than blending and cigarette making. All of the information contained in that document is contracted out to universities. None of it was done within the R&D group, as you inferred earlier on.

16:07:20 Q. Was that work --

16:07:36 MS. FORBES: And so the record is clear, I just have a continuing objection to any reliance on this document, and it does not constitute a waiver of our privilege.

MR. SOBOL: I'm not asking him about the

16:07:48 document.

Q. Did R.J.R. Tobacco International contract research regarding the health effects of smoking?

A. I don't remember the specifics, but my 16:08:10 recollection is that most of what they contracted was behavioral-type studies.

Q. Can you name for me one study regarding the health effects of smoking that was done by, or on behalf of, R.J.R. Tobacco International which was 16:08:42 shared with R.J.R. Tobacco domestically after your conversation with Dr. Di Marco.

A. To the best of my knowledge, there were no health-related studies, so I couldn't tell you whether or not they were shared. I know the others 16:08:56 were shared with us.

Q. And by "others," do you mean other nonhealth-related issues?

A. Those that had to do with the various biobehavioral-type things they were doing.

16:09:12 Q. Do you know whether or not, prior to your discussion with Dr. Di Marco, R.J.R. Tobacco International engaged in any research regarding the health effects of smoking?

A. No, I don't.

16:09:24 Q. Do you remember whether or not it was done in their behalf?

A. No, I don't.

Q. The behavioral-type studies which you say R.J.R. Tobacco International engaged in, did they include research regarding nicotine addiction?

16:09:54

MS. FORBES: Objection. Lack of foundation, assumes facts not in evidence, vague.

A. I'm not sure I understand nicotine addiction, but the studies that were carried on were, to the best of my recollection, were studies where people were playing card games and smoking cigarettes and being observed. That's one example of one that I remember.

16:10:10

16:10:26 Q. You are not familiar with the term "nicotine addiction"?

MS. FORBES: Objection. Misstatement.

A. I'm familiar with the term.

Q. What is your understanding of what that term means?

16:10:34

A. My understanding of the term "addiction" is that you are physically, and not merely psychologically, dependent upon a drug. And a study was done at Bowman Gray School of Medicine which

16:11:08 showed that nicotine fell at the level of caffeine on a scale of about ten compounds and cocaine and heroin with the other end. Those are the kinds of drugs I would classify as addictive, whereas
16:11:26 caffeine and nicotine fall in the physiologically dependent area -- or psychologically, excuse me -- dependent area.

Q. Do you know whether or not R.J.R. Tobacco International engaged in research regarding whether
16:11:38 or not nicotine was physically, not psychologically dependent inducing on smokers?

A. Would you repeat that question.

Q. Did R.J.R. Tobacco International engage in research to determine whether or not smokers became
16:11:56 dependent physically on nicotine?

A. I would not know. No, I don't know.

Q. Are you familiar with the term "nicotine dependence"?

A. Yes.

16:12:10 Q. Is that, is your understanding of nicotine dependence different than your understanding of nicotine addiction?

MS. FORBES: Objection. Vague.

A. Yes.

16:12:16 Q. What is your understanding of nicotine dependence?

A. Very much like caffeine dependence.

Q. Okay. Well, can you describe it for me and

16:12:24 the jury.

A. For whom?

Q. We are taking testimony here.

A. Describe caffeine dependence?

Q. Yes -- no. Describe nicotine dependence.

16:12:40 A. It's -- the best I understand it, it's just like a caffeine dependence where people enjoy it but can quit if they choose.

Q. Do you know whether or not R.J.R. Tobacco International was engaged in research regarding

16:13:06 nicotine dependence?

A. No, I don't.

Q. As the person heading the Biochemical Biobehavioral Division of R&D at R.J.R., do you believe that if such research regarding nicotine

16:13:28 dependence or nicotine addiction was being conducted at R.J.R. Tobacco International, you would have been made aware of it?

MS. FORBES: Objection. Compound, vague.

A. I would hope so, and I think I would have

been.

(Document marked as Hayes Exhibit 5 for identification)

Q. Exhibit No. 5, Dr. Hayes, is a memo dated October 30, 1984, entitled "Development and Application of Computerized Methods for Analyzing Nicotine Binding Models."

MS. FORBES: For the record, this document has a legend stating that it's confidential, subject to confidentiality order of the United States District Court, Eastern District of Texas, Texarkana Division, and was produced by R.J.R. pursuant to that confidentiality order in the Texas A.J. case. It is privileged -- it is not privileged --

MR. HOLTON: No.

MS. FORBES: -- as far as we are aware, but it is subject to that confidentiality order.

MR. SOBOL: Well, it's also my understanding, Ms. Forbes, that our confidentiality order in the California case, which I brought with me for people to execute, would accommodate those confidentiality concerns that were in place in the Texas litigation.

BY MR. SOBOL:

16:16:22 Q. Have you had a chance to briefly familiarize yourself with the document, sir?

A. Yes.

Q. Do you recall seeing this document before?

16:16:30 A. No.

Q. Why don't you look on the second-to-last page under "Distribution."

A. Yes.

Q. Do you see your signature there?

16:16:46 A. Yes.

Q. That's a copy of your signature?

A. Yes.

Q. For what purpose would you have executed this document under "Accepted"?

16:17:04 A. I don't specifically remember the procedure that we had at this time, but this may have been part of the "good laboratory practices" procedure that we instituted which required checkoffs to be sure that the data were verifiable.

16:17:30 Q. That's it?

A. Yes.

Q. Before you would have put your signature here under "Accepted," would you have reviewed the document?

16:17:38 A. I would have read it.

Q. You would have determined that the data in there was verifiable?

A. I would have determined that the data, at
16:17:56 least the written part, not necessarily the mathematical equations, were verifiable.

Q. All right.

A. But the approval was by John Reynolds, so he would have done that.

16:18:12 Q. Were you accepting his approval?

A. Yes.

Q. Let's look at the first page. Do you recall Project No. 7610 regarding smoker behavior?

A. No.

16:18:32 Q. On October 30, 1984, were you the head of the Biochemical Biobehavioral R&D?

A. Yes.

Q. And at that time Dr. Reynolds would have been reporting to you regarding the work done by the
16:18:46 Biobehavioral Division?

A. Correct.

Q. Do you remember the work being done to develop and apply computerized methods for analyzing nicotine binding models?

16:18:58
A. Vaguely.
Q. Was this done in connection with Premier?
A. The ultimate purpose may have been for Premier, but a lot of this was just very good basic
16:19:18 science, and all of this has been published in the open literature.
Q. Lippiello and Chamberlin had it published?
A. To the best of my recollection.
Q. As a document coming out of R.J.R. and its
16:19:38 Biobehavioral Division, you would have reviewed it prior to publication?
A. That's correct.
Q. To determine whether or not it had any scientific merit?
16:19:54 A. Yes. And obviously it had good scientific merit because it was accepted for publication in a peer review journal.
Q. Do you know what "binding properties" of nicotine refers to?
16:20:10 A. Only vaguely.
Q. What is your understanding?
*A. That in order for any chemical to exert a biological effect, it has to interact at a receptor site or a binding site.

16:20:42 Q. And does it interact with a receptor or binding site -- I'm sorry.

MR. SOBOL: Can you read the answer back for me.

(*Answer read)

Q. What is a binding site?

A. If I knew that, I would have a Nobel prize.

Q. What is a receptor site?

A. If I knew that, I would also have a Nobel
16:21:22 prize.

Q. How is it that nicotine interacts with the binding site? Another prize?

A. There are probably people that understand
16:21:48 it a lot better than I do. It's a chemical, either van der Waals' forces, covalent bonding, some type of interaction between the biological site and the chemical molecule.

Q. Why would R.J.R. be interested in the binding properties of nicotine?

16:22:10 A. A lot of the type of work that Lippiello and his colleagues were doing was to try to understand binding sites, receptor sites, and nicotine is a very good model compound to use in those kinds of studies.

16:22:32 Q. What makes nicotine a good model compound?

A. Probably the best reason it's a good compound is that literally thousands of other people have used it in studies, so there's a tremendous

16:22:44 amount of background information to build on.

Q. What other model compounds has R.J.R. investigated to determine how it interacts with binding sites or receptor sites in order to create a biological effect?

16:23:10 MS. FORBES: Objection. Vague and ambiguous.

A. I don't recollect, but Pat Lippiello would know the answer to that.

Q. The only one which you can recall is

16:23:18 nicotine; is that correct?

A. I know I used other compounds, but that's the only one I can recall because you refreshed my memory.

Q. What other compounds in cigarette smoke of

16:23:40 which you are aware create a biological effect through the interaction with binding sites or receptor sites?

MS. FORBES: Objection. Overbroad.

A. There are some -- I can't remember the

16:23:54 number -- 3,000 plus chemicals in cigarette smoke. I would wager that all 3,000 of those will bind to some receptor site if they are going to induce a biological effect.

16:24:14 Q. You are sure that Lippiello and Chamberlin were investigating other compounds to determine their biological effect through interacting with binding and receptor sites?

A. To the best of my recollection.

16:24:24 Q. And did it publish that work too?

A. I don't remember.

Q. There's no particular interest that R.J.R. had in nicotine?

MS. FORBES: Objection.

16:24:42 Q. It's just one of those good model compounds it decided to investigate?

MS. FORBES: Objection. Asked and answered, argumentative.

A. Yes.

16:24:54 Q. Do you know what a neuroblastoma cell is?

A. Specifically, no; generally, yes.

Q. What is your general understanding?

A. It is a specific brain cell that has been grown in culture.

16:25:20 Q. For the purpose of research such as this?
A. Correct.
Q. Do you know whether or not this study led to any specific design characteristics of the
16:25:52 Premier cigarette?
MS. FORBES: Objection. Vague.
A. Not to my recollection.
Q. How was this study to assist in the preparation of the Premier cigarette?
16:26:06 MS. FORBES: Objection.
A. As I've indicated earlier, my recollection is that this was to understand the mechanisms involved in receptor binding using nicotine as a model compound.
16:26:26 Q. And -- okay. Well, why is it that R&D was spending its time understanding this aspect of nicotine?
MS. FORBES: Objection. Asked and answered.
16:26:38 A. One of the things that any good research organization, regardless of whether it's industry, government and academia, allows their scientists to do is basic research to try to understand the underlying mechanisms, and this is one of those

16:26:56 areas where that was being done.

(Document marked as Hayes Exhibit 6 for identification)

Q. Exhibit No. 6 --

16:27:28 MS. FORBES: If you would just give me a minute before you start examining to take a look at this document so I can make a determination.

MR. SOBOL: This is a document dated January 7, 1985, from Dr. Burger to you regarding

16:27:48 your trip to CTR.

(Witness reviews document)

MS. FORBES: Either we will need to take a break so I can make a privileged determination on this or defer it to tomorrow when I have that

16:28:18 information easily accessible, however you want to proceed, take a beak or examine, because it's clear from the face that this document involves a meeting with counsel for R.J. Reynolds.

MR. SOBOL: You may recall that this was an

16:28:34 exhibit at Dr. Burger's deposition.

MS. FORBES: I did not attend Dr. Burger's deposition.

MR. SOBOL: Oh, you are right.

MS. FORBES: So I can't participate.

16:28:42 Mr. Maistros and I had this.
MR. MAISTROS: Mr. Belasic didn't make any
objection to this document, but you can call and ask
him.
16:28:52 MS. FORBES: Take a break, or you can --
MR. HOLTON: This will probably take a few
minutes. I can do it from here.
MR. SOBOL: Fine.
THE VIDEOGRAPHER: Off the record at 4:28.
(Recess taken)
THE VIDEOGRAPHER: Back on the record at
4:31.
MS. FORBES: Mr. Sobol, it's my
understanding there's not a privileged claim to this
16:31:42 document.
BY MR. SOBOL:
Q. Do you recognize this document?
A. No.
Q. Do you recall going to Council for Tobacco
16:31:56 Research office in New York in December of 1984?
A. No.
Q. Do you recall making a trip to New York at
all in December of 1984 with Dr. Burger?
A. No.

16:32:10 Q. Do you recall having been at CTR's offices in New York at any time?

A. No.

Q. Do you know what CTR is?

16:32:24 A. Council for Tobacco Research.

Q. Who are they? What do they do?

A. I think that they were the group that funded research for the tobacco industry.

Q. What kind of research?

16:32:50 A. Again I've seen their booklets, general basic research, applied research such as this one.

Q. I'm sorry. Did you say that the tobacco industry funded research conducted by CTR?

A. No. The tobacco industry -- the Council

16:33:20 for Tobacco Research was the funding organization, and the tobacco industry pooled its money together so that this organization could fund both basic and applied research.

Q. At any time during your employment at

16:33:40 R.J.R., did you make a request that CTR conduct certain kinds of research?

A. No.

Q. At some point CTR ceased to exist, if you understand me?

16:33:58 A. Only based on what I have read in the newspaper as a result of some agreement with one of the states. I understood that it was going to go out of existence.

16:34:22 Q. Okay. Do you recall this particular study referred to in the Document No. 6?

MS. FORBES: Objection. Vague.

A. The Carol Henry study?

Q. Yes.

16:34:32 A. Yes.

Q. And was that a study that was funded by R.J.R.?

A. It was funded by the Council for Tobacco Research with R.J.R. as one of the participating 16:34:48 members of the council.

Q. And do you recall why it is that you and Dr. Burger had a role in that bit of research?

MS. FORBES: Objection to form.

A. We had no role in that research. It was 16:35:10 completed prior to our arrival at R.J.R., if I remember correctly.

Q. Do you recall that there were problems discussed with the write-up of her research?

MS. FORBES: Objection. Vague.

16:35:28 A. The problem that I remember about her research was that she was having a very difficult time in finding the time to write it for publication in the peer review literature. And reading this, 16:35:54 Dr. Burger made the suggestion that we develop a consultant to help her with the preparation of this manuscript as long as we did not dictate or influence. And I'm quoting the author's interpretation of the data.

16:36:14 Q. Okay. Dr. Henry's work was a chronic mouse study?

A. That's my recollection.

Q. What is a chronic mouse study?

A. Grater than one year. Probably approaching 16:36:24 18 months to two years.

Q. Do you remember the nature of that particular study?

A. I'm trying to remember if it was an inhalation study; and I think it was an inhalation 16:36:38 study, but I'm not sure.

Q. What was investigated as part of that inhalation study?

A. Without seeing the full report or the published report, I don't -- I couldn't answer that

16:36:50 question.

Q. It was to determine whether or not the mouse got a disease by virtue of exposure to tobacco smoke?

16:37:20 A. I don't remember, and I don't see it here as to what the hypothesis of the study was.

Q. Do you see in the middle of the document where Dr. Burger has stated, "As a solution to those concerns, Dr. Hayes suggested that a 'ghost writer' 16:37:48 be hired to expedite the completion of the manuscript for publication"?

A. Correct.

Q. Do you recall making that suggestion?

A. No, but it wouldn't surprise me that I did.

16:38:00 Q. Do you recall discussing the items of the report regarding her writing style that could be easily interpreted in several ways?

MS. FORBES: Objection. Vague.

A. No, I don't recall that.

16:38:14 Q. Was that one of the things that you suggested there be a ghost writer for?

MS. FORBES: Objection. Vague.

A. No. The reason I suggested a ghost writer was so that we could help her get this manuscript

16:38:28 into the public arena.

Q. Okay.

A. My purpose was not to deny the scientific community this study.

16:38:44 Q. Do you see where Dr. Burger says, "Items in the report that were discussed included"?

A. Uh-huh.

Q. I want you to read that full sentence into the record.

16:38:54 A. "Items in the report which were discussed included writing style that left some paragraphs easily interpreted several ways; high mortality of animals in first chronic study; depletion of," and it may be "restraint."

16:39:14 MS. FORBES: I think that's "depiction."

THE WITNESS: "Restriction"?

MS. FORBES: "Depiction."

MR. KEHOE: "Depiction."

THE WITNESS: It's r-e.

16:39:20 Q. The word before.

A. Oh, "depiction of" -- I don't know what that word is -- "of laboratory mice such that overt stress is implied; confusion over dosimetry issues; dose of one milligram TPM per mouse roughly equals

16:39:46 250 cigarettes a day in man and not typical of the average smoker or even the heavy smoker; and need to publish as a series of articles in refereed journals the information found in this study."

16:39:56 Q. Do you remember any of those items being discussed?

A. No.

Q. The next sentence is, as a solution to those concerns," which you just read into the

16:40:06 record, you suggested that a ghost writer be hired. Is that consistent with your memory of what occurred?

MS. FORBES: Well, in fairness, the full sentence says "to expedite completion of the

16:40:20 manuscript for publication."

MR. SOBOL: Okay.

A. "Be hired to expedite completion of the manuscript for publication." That was the whole purpose of it.

16:40:28 Q. It wasn't to address those concerns that were just listed in the previous sentence; is that your testimony?

MS. FORBES: Objection. Argumentative.

A. Those concerns should be addressed, for

16:40:40 example, if there was an issue over dosimetry, that had to be sorted out, because that's key.

Q. Was that going to be sorted out by the ghost writer?

16:40:50 A. If you go down and you read, it says that as long as R.J.R. did not dictate or influence the author's interpretation of the data, there should not be a problem with this approach. I think that makes it very clear that there was to be no

16:41:06 interference, only to be sure that the data reflected what actually occurred.

Q. Do you know if Carol Henry's study was published?

A. I don't remember, but I don't think that it was.

Q. Do you recall a reason why it was not?

A. No.

Q. Do you recall whether or not a ghost writer was found?

16:41:30 A. No.

Q. "No, one was not found," or "no, you don't recall"?

A. I don't recall.

Q. Do you know whether or not R.J.R. kept a

16:41:48 copy of her report that you reviewed with Dr. Burger?

MS. FORBES: Objection. Lack of foundation.

16:42:02 A. I don't know if R.J.R. kept a report, but I know that Dr. Burger reviewed the report.

Q. I'm referring you down a few sentences, sir. It says, "It was felt by all of those present that this study needs to be presented to the

16:42:36 scientific community in lieu of the results." Do you recall that being discussed?

A. Where are we now?

Q. Take your time to find it. It's a few sentences down after the "ghost writer" sentences.

16:42:48 A. The first paragraph?

MR. KEHOE: Yes, about an inch and a half up from the bottom on the far right-hand side. "It was." Right over here. "It was."

A. I don't know what that sentence means.

16:43:30 Q. My question was a little bit different. It was whether or not you recall it being discussed that the report, as drafted by the ghost writer, should be reported in lieu of the results.

MS. FORBES: Objection. That misstates and

16:43:44 mischaracterizes, and he testified he doesn't know what the sentence means.

A. One, I don't know what the sentence means, and, two, I don't even remember the meeting.

16:43:58 Q. Do you see down in the next paragraph referring to you and Dr. Burger attending a meeting of the board of CTR?

A. Uh-huh.

Q. Do you know who the board members were?

16:44:12 A. No.

Q. And you don't recall that aspect of your meeting either?

A. (Witness shakes head)

Q. I'm sorry. I asked you, you couldn't

16:45:00 recall that aspect of the meeting?

A. No.

Q. Your trip to... How many times did you travel to New York on behalf of R.J.R.; do you know?

A. No.

16:45:10 Q. Was it many times?

A. A number of times.

(Document marked as Hayes Exhibit 7 for identification)

Q. Take a look at Exhibit 7, please. It's

16:46:04 from Microbiological Associates to you.

(Witness reviews document)

Q. Have you had a chance to review the document, sir?

16:47:46 A. Yes.

Q. Do you recognize it?

A. Yes.

Q. What is it?

A. It's a document from Carol Henry to me.

16:47:56 Q. Who is Carol Henry?

A. She is a toxicologist who at that time was the director of Inhalation Toxicology at Microbiological Associates in Bethesda, Maryland.

Q. She encloses to you an outline of the

16:48:18 position paper entitled "Approaches to Toxicological Evaluation of Whole Tobacco Smoke." Do you see that?

A. Uh-huh.

Q. Is that the same document which is referred

16:48:30 to in the previous exhibit that you and Dr. Burger reviewed; do you know?

A. No, it's not.

Q. What was the "Approach to Toxicological to Whole Tobacco Smoke" about?

16:48:46

A. At this time there was no general, overall document in the peer review literature that covered all of the animal studies that had been undertaken using whole tobacco smoke by inhalation.

16:49:12

Q. Did you give her the proposal outlined in this letter your approval?

A. We did not do it because IARC subsequent to this came out with their document, which basically did what she had outlined to do, so there was no need to duplicate that document.

16:49:26

(Document marked as Hayes Exhibit 8 for identification)

Q. Would you take a look now at Exhibit No. 8, sir.

16:49:46

(Witness reviews document)

Q. Have you had a chance to familiarize yourself with the document?

A. Yes, briefly.

Q. Now --

16:51:08

A. I made a mistake. What I told you was not correct on this document. This document was when we were trying to come up with the best possible approach to evaluating Premier, she was one of the people we asked to give us their opinion as to how

16:51:28 such a study could be carried out.

Q. You are referring, sir, to Document No. 7?

A. That's Document No. 7, which is now what Dr. Burger reminded me what 7 is about.

16:51:44 Q. In fact, the first sentence indicates that Microbiological Associates did in fact conduct that work for you?

A. They prepared a document that offered suggestions as to how one might evaluate whole

16:52:06 tobacco smoke, and this was ultimately going to be programmed into the Premier project.

Q. Do you recall seeing this document before today?

A. The Burger document?

16:52:34 Q. Yes, Exhibit No. 8.

A. I'm sure I did. It was sent to me.

Q. Do you recall that?

A. No.

Q. Do you recall whether or not Dr. Burger's

16:52:48 suggestions regarding their report were put into effect?

A. I would think that the vast majority of his suggestions were put into effect and that in the end we probably rejected a number of the Microbiological

16:53:10 Associates' suggestions.
Q. What were you -- what was to be done with
this paper they prepared after it was done?
A. We are talking about the Microbiological
16:53:20 Associates?
Q. Yes.
A. It was simply a paper along the lines that
if you are going to build a bridge across a river,
you might ask a half a dozen people to give you
16:53:38 their suggestions, and then you incorporate the best
and end up with the best bridge you can possibly
make. And that's what we were trying to do is
develop the best protocol that we could develop for
this comparative toxicology study with Premier and
16:53:54 the Kentucky reference cigarettes.
Q. Was it your understanding that the document
prepared by Microbiological Associates was going to
be part of that which would be eventually published
by R.J.R. in the Premier monograph?
16:54:10 A. I don't think that we are communicating
yet.
Q. Okay.
A. This document that Microbiological
Associates prepared was, "here are our thoughts as

16:54:28 to how you might carry out this program based on the input from Dr. Burger." And he says that two members of the Toxicology Research Division also put in some comments, and based on that it would appear
16:54:44 that we rejected the vast majority of the suggestions that were offered by Microbiological Associates.

Q. All right. I want to direct your attention to a sentence that appears in the middle of the
16:55:00 first paragraph on Page 1. It begins -- I'll read it for you, and you can find it if you need to put it in context. "That is, they should limited their discussion to a review of the animal research in tobacco smoke with very little reference to
16:55:16 epidemiology studies." Do you see that?

A. Yes.

Q. All right. Does that indicate to you, sir, that Dr. Burger was giving Microbiological Associates advice on how to redraft their document?

16:55:40 MS. FORBES: Objection. Misstates, mischaracterizes.

A. No, that just tells me that Dr. Burger has reached the same conclusion that I would reach: Let's stick to what we are going to do, animal

16:55:56 studies.

Q. And delete reference to epidemiologic studies?

A. Since we are only going to be doing
16:56:10 experimental animal studies, we do not need protocols for doing epidemiology studies.

Q. So when he says they should limit their discussion, he is not referring to them making changes in their document?

16:56:24 MS. FORBES: Objection. Argumentative.

A. You might ask him. I would interpret it that he is not making that suggestion. He is telling me let's keep it, limit it to what we are going to do.

16:56:52 MR. SOBOL: It's 5:00. Do you want to have a talk about how we are going to proceed today?

MR. KEHOE: Yes, off the record.

THE VIDEOGRAPHER: Off the record at 4:57.

(Discussion off the record)

16:57:32 THE VIDEOGRAPHER: Back on the record at 4:57 p.m.

BY MR. SOBOL:

Q. Okay. Let's look at Page 2, sir, okay? And do you see where it says --

16:57:52 MR. KEHOE: Mike, I want to change my mind. I'm tired. I think he is tired. It's 5:00.

MR. SOBOL: That's fine with me.

MR. KEHOE: Okay.

16:58:02 MR. SOBOL: You are the one who suggested we go later. Do you want to stop now?

MR. KEHOE: Yes.

MR. SOBOL: Fine. Begin tomorrow at 9:30.

THE VIDEOGRAPHER: Off the record at 4:58.

(Whereupon the deposition was suspended at 4:58 p.m.)

CERTIFICATE

I, A. Wallace Hayes, do hereby certify that I have read the foregoing transcript of my testimony, and further certify that said transcript (with/without) suggested corrections is a true and accurate record of said testimony.

Dated at _____, this ____ day of _____, 1998.

_____

Sworn and subscribed to before me this ____ day of _____, 1998.

_____

Notary Public

My commission expires:

_____

- - - -

COMMONWEALTH OF MASSACHUSETTS)
SUFFOLK, SS.)

I, Nancy M. Kingsbury, Registered Professional Reporter and Notary Public in and for the Commonwealth of Massachusetts, do hereby certify that there came before me on the 3rd day of June, 1998, at 11:46 a.m., the person hereinbefore named, who was by me duly sworn to testify to the truth and nothing but the truth of his knowledge touching and concerning the matters in controversy in this cause; that he was thereupon examined upon his oath, and his examination reduced to typewriting under my direction; and that the deposition is a true record of the testimony given by the witness.

I further certify that I am neither attorney or counsel for, nor related to or employed by, any attorney or counsel employed by the parties hereto or financially interested in the action.

In witness whereof, I have hereunto set my hand and affixed my notarial seal this 19th day of June, 1998.

Nancy M. Kingsbury
Notary Public

My commission expires 12/21/2001

Hayes #1

DRAFT

DETERMINATION OF NICOTINE DOSE DELIVERED DURING HUMAN SMOKING. J H Robinson, J D Dethiziy, R A Davis, D W Griffith, J H Reynolds and A W Hayes. R J Reynolds Tobacco Company, Winston-Salem, NC.

The 'tar' and nicotine values that are determined by the Federal Trade Commission (FTC) machine smoking method do not always reflect the amount of NIC delivered to or absorbed by an individual smoker. We have integrated a series of research techniques that enables us to determine NIC delivered during human smoking and to apply these techniques to the study of NIC pharmacokinetics. These include the measurement of puff parameters during cigarette smoking (volume, duration, rate, shape, number and intensity of puffs), breathing patterns before, during and after smoking (inspiratory/ expiratory volume, rate, time) and plasma NIC concentrations during smoking. We have also developed a programmable smoking machine that rereproduces the measured human puffing patterns, allowing for subsequent replication of these patterns and chemical analyses of the generated smoke. We studied 4 males, who each smoked 7 commercially available cigarettes. NIC area under the plasma curve (AUC) ranged from 339 - 941 ng/ml and as expected, was significantly correlated with number of puffs (x=11.6) and average time of smoke inhalation (x=1.57 s). Unexpectedly, NIC AUC was negatively correlated with averaged puff volume and puff intensity measures. NIC delivery ranged from 0.96 to 2.48 mg compared to an FTC determined delivery of 0.71 mg. These techniques are essential to the determination of the pharmacokinetic properties of NIC derived from cigarette smoking.

Hayes #2

DRAFT

INTEROFFICE MEMORANDUM

TO: Dr. A. W. Hayes

FROM: J. H. Reynolds

SUBJECT: Status Report, 4th Quarter, 1985
Biobehavioral Research Division

DATE: January 16, 1986

Attached is the Quarterly Status Report for the Biobehavioral Research Division, based on Plan Objectives as stated in the 1985 Biobehavioral Division Action Plan.

Distribution:

Ms. S. L. Jowdy

Plan Objective 1. Develop/improve means to accurately determine doses of smoke components to smokers and relationships of smoking behavior patterns to product properties.

A. Continue development of human-mimic smoking machine.

The most recent version of software for "massage" of puff profile data for the human mimic smoking machine (HMSM) was translated and installed on the HP-1000 E-series computer. The software was developed jointly by Mr. Chamberlin and Dr. Sears (Fundamental R&D). This software was tested and was found to work accurately. Final enhancements will be made to the software to achieve the best replication of human puffs possible with this type of massage. At this time selected, single puffs can be "massaged", but if testing confirms expectations of performance, extension to multipuff replication will be relatively easy. A 208V power outlet installed in room 112 of building 611-12 to accommodate the HMSM. Preparations for the installation of the human olfactometer in room 114 necessitate this move.

B. Continue analysis of previously collected human smoking data and collect new data as needed.

Analysis of data generated in a study of WINSTON and Marlboro smokers continued. Simultaneous measures of puff profile parameters, breathing behavior and plasma nicotine concentrations were obtained. Last quarter, it was reported that breaths taken immediately following puffs of a cigarette were significantly different from other breaths in several respects, namely inspiratory time and volume, expiratory time and volume and respiration frequency. It was also reported that there were no statistically significant differences in the plasma nicotine concentrations found during or following smoking which were owing to the cigarettes smoked.

The continuing analyses of these data have focussed on two major areas. First, the exploration of the dependency of plasma nicotine concentrations on puffing and/or breathing behaviors, and second, the examination of the "after-puff" breaths to determine how they relate to either the smoker or the cigarette smoked.

As reported last quarter, changes in nicotine concentrations in the plasma of smokers were similar whether the cigarette smoked was WINSTON or Marlboro. Although the puff profile data from this experiment have not been rigorously analyzed, previous data collected from WINSTON and Marlboro smokers showed no statistically significant differences related to the kind of cigarette smoked. That is, although individuals are different from one another in puffing behavior and in plasma nicotine concentrations attained, the cigarettes smoked do not appear to be associated with consistent, significant differences in these variables. However, the most recent analyses of the data indicate that, if consideration is restricted to only one cigarette and only one subset of smokers (i. e. WINSTON smokers or Marlboro smokers) at a time, remarkably precise predictions of the maximal changes in plasma nicotine concentrations can be made on the basis of puffing and breathing parameters.

Herning, et al. (Clin. Pharmacol. Ther. 33(1), 84-90 (1983)) reported multiple regressions of the natural log of the change in plasma nicotine concentration from 1-2 min. before smoking to 0.5 to 2 min. after smoking. Their subjects included 11 regular smokers of a low-tar cigarette (reportedly ca. 1.0 mg/cig). The independent variables used by these workers were cigarette nicotine yield (two differing cigarettes were used), interpuff interval, number of puffs, puff volume, puff duration, inhaled volume, and duration of inhalation. The multiple R (regression coefficient) reported by them was 0.93.

Our results are based on a linear regression, rather than a log-linear regression and show improved multiple regression coefficients. Nicotine yield was not used in our regressions, since the WINSTON and Marlboro were not widely different in nicotine yield (WINSTON 1.30 mg/cig, Marlboro 1.27 mg/cig, banded cigarettes). In addition our results seem to indicate that smokers of different brands employ subtly different smoking strategies, that these may change when different cigarettes are smoked and that they may not be reflected in overall comparisons of puffing parameters alone, especially when cigarettes of very similar properties are studied.

It should be emphasized that our results are so far based on a small data set (13 smokers) and need replication and expansion. The next steps in this work will focus on these needs.

The data were analyzed by stepwise linear multiple regression. The dependent variable was the the maximal change (from baseline) in plasma nicotine concentration observed for the individual. Independent variables for each individual were as follows:

PVOL	Average puff volume
BPM	Breaths per minute
INVOL	Average inspiratory volume
INTIM	Average inspiratory time
MINVOL	Average minute ventilation
EXTIM	Average expiratory time
EXVOL	Average expiratory volume

All breathing data were based on only those breaths which immediately followed puffs. The puff volume was averaged over the whole cigarette.

The data were segregated into several groups, based on the cigarette smoked and the reported regular brand of the smoker. The results of the multiple regression analyses are shown in the table on the next page.

RESULTS OF MULTIPLE REGRESSION ANALYSES

WINSTON Smokers, Smoking WIN3TON

Independent Variable	Multiple R	R Square	Change in R Square	Simple R
INTIM	0.31	0.098	0.098	- 0.31
PVOL	0.57	0.33	0.23	0.25
MINVOL	0.69	0.48	0.15	- 0.19
EXTIM	0.75	0.57	0.09	0.14
INVOL	0.999	0.999	0.43	- 0.29

WINSTON Smokers, Smoking Marlboro

Independent Variable	Multiple R	R Square	Change in R Square	Simple R
INTIM	0.75	0.56	0.56	- 0.75
PVOL	0.89	0.79	0.23	0.51
MINVOL	0.97	0.94	0.15	0.12
EXTIM	0.99	0.97	0.04	- 0.27
INVOL	0.99	0.98	0.001	- 0.38

Marlboro Smokers, Smoking WINSTON

Independent Variable	Multiple R	R Square	Change in R Square	Simple R
INTIM	0.77	0.59	0.59	0.77
PVOL	0.996	0.99	0.40	0.65
EXTIM	0.997	0.99	0.002	- 0.12
BPM	0.998	0.996	0.001	- 0.28

Marlboro Smokers, Smoking Marlboro

Independent Variable	Multiple R	R Square	Change in R Square	Simple R
PVOL	0.86	0.74	0.74	0.86
EXVOL	0.91	0.83	0.089	- 0.40
INVOL	0.93	0.87	0.039	- 0.65
INTIM	0.998	0.996	0.13	0.45

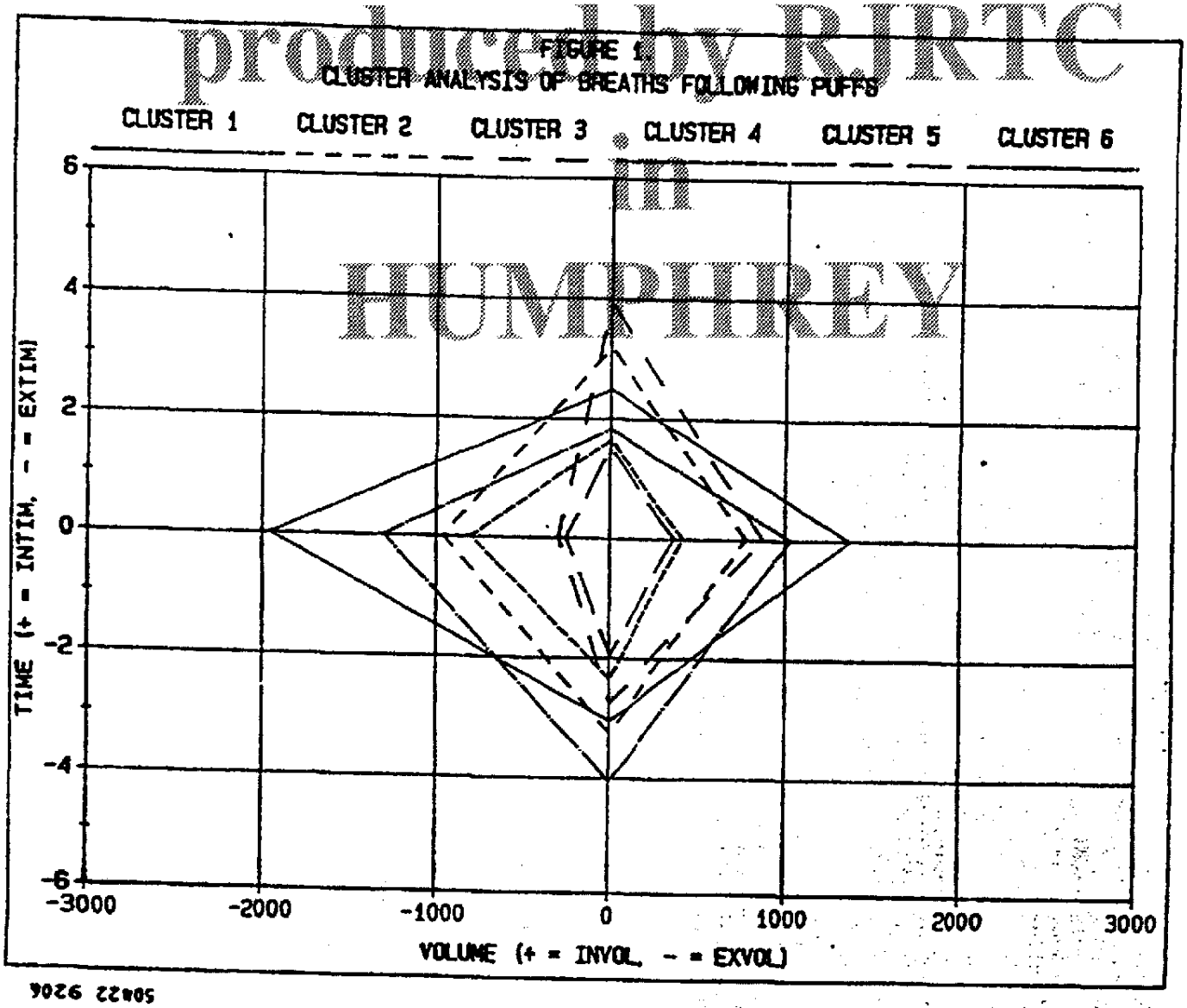
(continued on next page)

The examination of the breath data has progressed as follows. Two hundred thirty-eight breaths were observed to immediately follow puffs. Of these, a random sample (143 breaths) was taken. A cluster analysis of these breaths was performed on the basis of four parameters; inspiratory time and volume, and expiratory time and volume. This work showed that clusters of breaths, internally similar to one another but different from breaths in other clusters, could be formed.

Owing to the clustering procedure used, the number of clusters is somewhat arbitrary. Analyses yielding from 2 to 16 clusters were performed. Inspection of these indicates that six rather different clusters can be discerned. These are represented graphically in the map shown in Figure 1. In this map, the respiration volumes are represented on the abscissa (with inspiration volumes taking positive values and expiration volumes taking negative ones). The respiration times are represented on the ordinate (with inspiration times taking positive values and expiration times taking negative ones). The mean values of respiration volumes for the clusters are plotted at zero respiration times, while the mean values of respiration times for the clusters are plotted at zero respiration volumes. Thus, each cluster appears in the form of a quadrilateral on the map. Inspection of the Figure reveals how the clusters differ from one another according to these parameters.

The next steps to be taken in this work will be to form discriminant functions capable of mathematically assigning breaths to clusters, processing all 238 "after-puff" breaths to assign them to clusters, determination of the within-smoker consistency of breath type, and the determination of the relationship of breath type to smoker's regular brand, to the brand actually smoked, to smoker's other breathing behavior, or to individual smoker's plasma nicotine concentrations.

FIGURE 1.
CLUSTER ANALYSIS OF BREATHS FOLLOWING PUFFS



Plan Objective 2. Develop knowledge/expertise in effects of tobacco product use on psychophysiological states of consumers.

A. Replace D. G. Gilbert.

During the third quarter of 1985 four candidates for the position of Sr. Behavioral Scientist, formerly held by Dr. D. G. Gilbert were interviewed. A formal offer of employment was made to one of these, Dr. W. S. Pritchard, of the University of Texas Medical Branch at Galveston. Dr. Pritchard declined the offer. A second candidate indicated that he was no longer interested in the position. The third and fourth candidates were found not suitable for the position. Subsequently, contact was made with a potential fifth candidate, but this person indicated no interest. A sixth candidate has been identified and will be contacted as soon as possible.

B. Complete reports covering Dr. Gilbert's work.

Dr. Gilbert was contracted in the third quarter as a consultant to R&D for the purpose of completing reports covering his work. He and Dr. C. D. Spielberger (consultant to Biochemical/Biobehavioral R&D) have made several visits to R&D for this purpose. They have maintained communication with one another and with Dr. John Robinson to organize and write these reports. At present a total of ten reports are expected to result from this effort. Their order of priority and status is as follows:

Proposed Title	Proposed Authors	Status
Effects of Smoking/Nicotine on Lateralization of EEG During a Stressful Movie.	D. G. Gilbert, J. H. Robinson, C. L. Chamberlin and C. D. Spielberger.	Ready for internal review in Jan. '86
Effects of Smoking on Heart Rate, Anxiety, and Feelings of Success During Social Interaction.	D. G. Gilbert and C. D. Spielberger	Ready for internal review in Jan. '86
Plasma Nicotine and Cortisol Concentrations Relate to Self-Reported Nausea and Anger: Cigarette Smoking as a Possible Stress-Reducing Behavior.	J. H. Robinson, D. G. Gilbert and J. H. Reynolds	Ready for internal review in Mar. '86
Effects of Smoking/Nicotine on Lateralization of EEG as a Function of Personality	D. G. Gilbert	Ready for internal review in May '86
Effects of Anxiety and Speaking on Heart Rate.	D. G. Gilbert and C. D. Spielberger	Ready for internal

		review in May '86
Effects of Nicotine and Stress on Heart Rate, Cortisol and Prolactin.	J. H. Robinson and D. G. Gilbert	Ready for internal review in June '86
EEG Spectra: Personality and Smoker/Nonsmoker Differences.	D. G. Gilbert	Ready for internal review in June '86
Personality, Hormones and Emotional Reactions.	D. G. Gilbert and J. H. Robinson	Ready for internal review in July '86
Effects of Smoking/Nicotine on Heart Rate and Emotional Reactions to a Noxie Stressor.	D. G. Gilbert and J. H. Robinson	Ready for internal review in Sept. '86
Effects of Nicotine on Facial and Autonomic Indicants of Stress as a Function of Personality.	D. G. Gilbert	Ready for internal review in Dec. '86

Plan Objective 3. Develop means to assess aspects of the blood chemistry of smokers; use these to determine psychophysiological effects of smoking in humans.

A. Provide nicotine/cotinine analyses as required.

Authorization was received for the purchase of an additional gas chromatographic system to increase the efficiency of the nicotine and cotinine determination. A purchase request was submitted for a delivery date of the equipment about January 15, 1986. Actual delivery will probably be in February.

Analyses of animal blood samples from both intra- and extra-mural work are being provided to the Toxicology Division. This work has been assigned a high priority and so has impact on Mr. Davis' ability to continue his work under Plan Objective 5.

B. Reports, publications, presentations and meetings.

A manuscript entitled "The Determination of Nicotine and Cotinine in Plasma" was submitted by Mr. Davis for publication in the Journal of Chromatographic Science. This work was also submitted as an internal report, R&DH No. 92, 1985.

An update of the status of this work was presented to the Scientific Advisory Board in October, 1985.

Plan Objective 4. Establish state-of-the-art program in nicotine receptor pharmacology. Develop/test hypotheses relating biochemistry of nicotine/neuron interactions to observable psychophysiological effects.

A. Rat brain membranes

1. Equilibrium binding studies.

a. Proteolytic inactivation.

Neutral proteases were tested for their ability to inactivate nicotine binding sites in rat brain membrane preparations. Collagenase and trypsin, with or without divalent cations present, did not change the equilibrium binding parameters (Bmax,Kd) even when incubated with membranes at 37 degrees C for 30 minutes. Since trypsin has been reported to release the binding sites into solution (by Abood et al.) it may be that the properties of the site are unchanged and the released protein is still trapped on filters during the binding assay. Other proteases are slated to be tested.

b. Pharmacological inhibitors.

Mecamylamine, a known nicotinic antagonist, was pre-incubated with brain membranes to determine the effects, if any, on nicotine binding properties. Scatchard analyses of the data showed that 100 uM mecamylamine reduced the Bmax by 50% and increased the apparent Kd to 12 nM. Additional studies will be conducted with other concentrations of the compound and with other known inhibitors.

c. Control experiments (miscellaneous).

The effects of buffer composition on nicotine binding properties were studied. TRIS buffer gave identical results to those obtained with HEPES buffer, with or without Ca++ and Mg++. The effect on nonspecific binding of using different concentrations of nicotine salicylate in 'blank' incubations was tested. The same results were obtained with 100 uM and 1 mM.

The purity of the L-[3H]nicotine ligand was checked by thin layer chromatography, and in collaboration with Dr. Dwo Lynn, by HPLC. The HPLC method, using the same solvent system as New England Nuclear, gave ca. 99% purity. However TLC with a different solvent system (used by Marks & Collins) showed several additional peaks, accounting for about 5% radiochemical impurity.

2. Binding kinetics.

The kinetics of binding of L-[3H]nicotine to rat brain membranes were studied in order to understand the mechanism of interaction of nicotine with receptor sites in the brain. It was found that the processes of association and dissociation could be described by a model previously proposed for the binding of acetylcholine to nicotinic cholinergic receptors in peripheral tissues (i.e. the neuromuscular junction). According to this model nicotine (N) can bind to either of two pre-existing receptor conformations, one having low affinity (R)

and the other high affinity (R') for nicotine, as follows:

$$N + R \underset{k2}{\overset{k1}{\rightleftharpoons}} RN$$

$$k8 \;||\; k7 \qquad\qquad k3 \;||\; k4$$

$$N + R \underset{k6}{\overset{k5}{\rightleftharpoons}} R'N$$

Both the unliganded (R,R') and liganded (RN,R'N) species can in turn equilibrate with one another, as shown above. This cyclic model is specified by eight rate constants (k1...k8). Initial estimates for these rate constants, based on experimental observation, were:

k1 = .04 /min/nM	k2 = 2 /min
k3 = .24 /min	k4 = .005 /min
k5 = .04/min/nM	k6 = .04 /min
k7 = .004 /min	k8 = .006 /min

These choices for the rate constants predict an overall equilibrium binding constant, Keq (= apparent Kd), of 2.4 nM in excellent agreement with the Kd of 2-3 nM consistently observed in equilibrium binding studies.

An analytical solution for this model was derived, in collaboration with Dr. Steven Sears (Fundamental R&D), and adapted to an HP-86 microcomputer to test the fit of the data to theoretical curves predicted by the model. Initial estimates for the rate constants yielded very good results. Manual iterative curve-fitting is being continued in order to achieve the best fit possible within experimental error limits. In general, all of the predictions of the model have been verified experimentally. Control experiments were also run at room temperature (ca. 22 degrees C) to be certain that the kinetics observed at low temperature (0 degrees C) were not due to binding artefacts. The results showed that the process of association was still biphasic as before. The on-rate was proportionally increased with temperature as expected.

Future studies will employ [3H]acetylcholine to determine if the kinetic binding properties are the same as those of nicotine or if the model is unique for nicotine binding.

B. Neuronal cell cultures.

1. Growth substrates.

Several different materials were tested for their ability to maximize cell adhesion to cell culture dishes. Fibronectin, collagen and poly-L-lysine (>.01%) were all found to be effective in promoting cell adhesion and in preventing cell detachment during binding assays.

2. Effects of nicotine on cell metabolism/function.

Preliminary experiments utilizing cultures from fetal rat brain showed some evidence of uptake of carbon-14 labelled 2-deoxyglucose. However, the specific uptake could not be reliably determined over the range of concentrations employed. It is felt that the specific radioactivity of the labelled compound was too low to provide good data. Material with a higher specific activity has been obtained. It is planned, once reliable data can be obtained, to explore the effects of nicotine at various concentrations on the metabolic activity of cultured cells via the 2-deoxyglucose technique.

3. Nicotine binding.

Equilibrium binding studies using membranes prepared from cultured neurons showed that the affinity of the sites for nicotine was the same as that for whole brain membrane preparations, with an apparent Kd of around 2 nM. However, over the first few days in culture, the maximum number of sites (Bmax) was only 10-20% of values observed in adult rat brain. Longer periods in culture (1-2 weeks) were sufficient for Bmax to return nearly to values observed in adult brain.

Equilibrium binding studies with intact cells gave apparent Kd values that were somewhat higher than usual (8-12 nM). There may be several reasons for this. For instance, the substrates used tend to alter cellular morphology by reducing the cellular aggregates normally seen on uncoated plates and reducing the numbers of cellular processes and interconnections. This may reflect selection for the growth of specific cell subpopulations. In addition there may be some uptake of nicotine by the cells even at low temperatures that would make accurate estimations of the Kd more difficult. Finally, the binding properties of nicotine to intact cells may be affected by diffusion barriers at synaptic junctions that would not be present in membrane preparations.

Binding experiments were begun using cells fixed with glutaraldehyde/paraformaldehyde since this procedure will be needed in subsequent autoradiography experiments. The fixation process does not appear to alter the receptor binding properties significantly and may actually help to reduce nonspecific binding.

C. Extramural research program.

1. University of Colorado.

Contact was made with Dr. Allan Collins, University of Colorado, to provide input for his research proposal to RJR in the area of genetic aspects of nicotine receptors in the brain. The experimental outline and budget were recieved January 7, 1986 and are under review.

2. University of Bath (U. K.).

Contact was made with Dr. George Lunt (U.of Bath) at the meetings of the Society for Neuroscience in Texas to discuss details of a research proposal to be submitted to RJR in the area of nicotine receptor purification/antibody production. An initial proposal was

delivered to RJR personnel at the nicotine symposium in Lexington, KY by Dr. Susan Wonnacott, outlining a collaborative effort with Dr. Lunt and Dr. Eric Barnard (Cambridge U.). Dr. Wonnacott was invited to BGTC to deliver a seminar and to hold detailed discussions on specific experiments that would be of mutual interest. The final proposal will take into account RJR input and is slated to arrive in mid-January, 1986.

3. Bowman Gray School of Medicine (BGSM).

Experiments using in vitro electrophysiological recording techniques are ongoing at BGSM. Dr. Deadwyler presented a progress report 12/12/85 to summarize data generated to date on both the hippocampal and hypothalamic projects.

Hypothalamus: An excitatory action of nicotine on neurones in these two hypothalamic areas has been identified. These actions seem to involve nicotinic acetylcholine receptors. However, the mechanisms which mediate these excitatory effects have not been identified. Personnel at BGSM are perfecting their intracellular techniques in hypothalamus to investigate these mechanisms over the next 12 months. However, Dr. Deadwyler has been concerned with the performance of the post-doctoral fellow working on this project and has decided not to renew this person's contract as of February 3rd. A search is underway to find a replacement.

Hippocampus: Recent experiments in this brain region have indicated that repeated applications of 80uM nicotine to cells in the CA1 pyramidal cell layer may result in effects that are not present or were overlooked with single applications. Intracellular experiments are currently underway to determine how robust these effects are. Dr. Deadwyler feels that only a few cells replicating this effect would be necessary for a manuscript on this finding. Whether or not this brain area will be pursued experimentally will depend on the results of the experiments being done now.

During his seminar Dr. Deadwyler also presented some preliminary data on possible nicotine effects in chronically prepared, behaving animals. These data were included to demonstrate possible future directions for our nicotine electrophysiology research. Drs. Hayes, Reynolds, Deadwyler and Robinson met after the seminar to discuss these future directions. It was generally agreed that the hippocampal and hypothalamic programs should continue as they have been, at least until the recent hippocampal data has been confirmed or disproved. Drs. Deadwyler and Robinson will cooperate on a proposal to be submitted in June or July of '86 to outline both chronic and acute experiments on nicotine through 1988. This proposal will be designed to complement the work done by Dr. Woodard (see below) as much as possible.

4. University of Texas.

Dr. Woodward's lab was visited by Dr. Robinson in October, 1985. Following the trip, several days were required to extensively re-work the various addenda to the proposal submitted by Dr. Woodward. Drs. Woodward and Robinson collaborated on the preparation of the final

proposal which was submitted and approved. The AR for this project received final approval on 12/20 and the contract with the University of Texas Health Sciences Center at Dallas (UTHSCD) was mailed 1/2/86. The proposed starting date for the research is 1/30/86.

D. Reports, publications, presentations and meetings.

An abstract entitled "The Binding of L-[3H]Nicotine to a Single Class of Sites in Rat Brain" was submitted and accepted for presentation as a poster session at the Annual Meetings of the American Society for Neurochemistry in Montreal, Canada (March, 1986). The abstract was sponsored by Dr. Stanley Prusiner, UCSF.

A manuscript entitled "The Binding of L-[3H]Nicotine to a Single Class of High Affinity Sites in Rat Brain Membranes" was submitted for publication in Molecular Pharmacology. This work was also submitted as an internal report, NIDH No. 94, 1985.

A manuscript entitled "The Kinetics of Binding of L-[3H]Nicotine to High Affinity Sites in Rat Brain Membranes" is in preparation.

The paper "Actions of acetylcholine and nicotine on neurones in the rat supraoptic and paraventricular nuclei" (Robinson et al.) was presented at the 15th Annual Meeting of the Society for Neuroscience and was published in the abstracts of the meeting (Soc. Neurosci. Abstr., Vol. 11, Part 2, 1235, 1985). A manuscript on the extracellular data reported at this meeting should be ready for review some time in the 1st Quarter '86. It may also be possible to generate a short note on the intracellular data collected on hypothalamic cells.

Trip reports were submitted for the meetings of the Society for Neuroscience (Dallas, TX) and are in preparation for the nicotine symposium held in Lexington, KY.

An update on status of all nicotine work was presented to the Scientific Advisory Board in October, 1985.

E. Miscellaneous.

Estimates are being obtained of costs associated with the installation of a cold room in building 611-13 to support the nicotine pharmacology program and of costs associated with the installation of a photographic dark room in the same building to support this program and the work of the Toxicology Division.

Plan Objective 5. Develop understanding of sensory modalities important to smokers and of relationships among sensory and chemical properties of smoke and smoking behavior.

A. Study of human odor perception.

Preparation of equipment and facilities for a study of the abilities of humans to perceive odors and irritation of some smoke constituents and other selected compounds continues. This work was begun in support of project SA and continues in support of the Environmental Tobacco Smoke Program.

All of the components (e.g. electronic mass flow controllers, electric solenoid valves, saturators) that have arrived have been installed on either the nasal or the ocular portion of the olfactometer. All of the electrical connections needed to connect the olfactometer to an AppleIIe microcomputer have now been prepared. The computer will schedule exposures and collect data. Dr. Walker is debugging the Applesoft BASIC program that will handle the operation of the olfactometer and the acquisition of psychophysical and physiological data.

Dr. Dan Kurtz (Technical Services) is securing additional furniture that will be needed for seating subjects and for mounting the eye and nose exposure apparatus. He is outfitting both the nasal and ocular portions of the olfactometer with the necessary Teflon plumbing.

A list of compounds proposed for use in the study was submitted to the Scientific Affairs Division for review. Sixteen compunds were approved initially and these are being ordered. Other compounds, whose use is at issue, will be reviewed with Dr. C. R. Green (Fundamental R&D).

B. Oral pH measurements in humans.

This experiment has now been completed. A synopsis of the basic findings was presented to R & D directors on December 17, 1985. With the exception of the puff profile results the data from this experiment have been analyzed in some detail. An internal report on this work will be forthcoming in the first quarter of 1986.

C. Pigeon anatomy and psychophysics.

All of the instruments and supplies that will be needed for doing surgery, histology and horse radish peroxidase (HRP) work on the pigeon have been accumulated. Ms. Miller is familiarizing herself with the use of HRP for neural tract-tracing. She is also familiarizing herself with the stereomicroscope and the photographic set-up and she and Dr. Walker will be doing a practice surgery within the next two weeks. Efforts toward setting up a pigeon odor psychophysical testing lab have been assigned a lower priority than the work with humans.

D. Reports, publications, presentations and meetings.

The abstract submitted in September 1985 to the American Association for Dental Research (AADR), entitled "Taste Perception and the Measurement of Intraoral pH" has now been corrected and the corrected version has been accepted. Dr. Walker is now a member of AADR and the international counterpart, IADR.

Drs. Walker and Kurtz (Technical Services) plan to attend the joint meeting of the International Symposium on Olfaction and Taste and the Association for Chemoreception Sciences in July, 1986. Abstracts of papers that they hope to present will be submitted for internal review.

Dr. Walker has continued work on several manuscripts describing research that he conducted prior to joining RJR. Comments on the manuscript entitled "Computerized Odor Psychophysics in Mice" have been received from Chemical Senses and some of the paper has been rewritten to accomodate the suggestions. Figures have been prepared for a paper titled "Psychophysical Comparison of Olfactory and Trigeminal Sensitivity to Several Odorants" to be submitted later this year. A manuscript titled "Photoperiodic Effect on Behavioral Response to Estrogen" will be prepared for submission to Hormones and Behavior.

Plan Objective 6. Support other areas of R&D and/or other Company areas as needed and approved.

A. New Product Technology

Investigations were planned, executed and reported as requested.

B. Law Department

Assistance was supplied as requested. This has mainly involved Dr. John Robinson, who has devoted a substantial amount of time working with attorneys in the defense of the smoking and health litigation.

C. Other

Assistance was provided to Applied and Brand R&D as requested.

Lectures on the work of the Biobehavioral Division were provided at two sessions of the Marketing Training Course. Lecturers included Drs. Lippiello, Robinson, Walker and Reynolds.

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R.J Reynolds Tobacco Company
Winston-Salem, N.C.

INTER-OFFICE MEMORANDUM

RJR

August 2, 1984

TO: Dr. G. R. DeMarco

SUBJECT: Weekly Highlights
Biochemical/Biobehavioral
Week of July 23, 1984

ITEMS OF GENERAL INTEREST TO R&D

Biobehavioral Research

1. Nicotine Pharmacology

a. Study of electrophysiology of nicotine

In this work, ongoing at the Bowman Gray School of Medicine, the study of the effects of pressure-ejection of small amounts of nicotine into specific areas of the hippocampus has begun. Excitatory responses, similar to those previously observed following introduction of nicotine salicylate via the bathing medium of the sample, have been observed.

b. Draft proposals for additional ex-house work have been received and reviewed. In the first, from Dr. S. A. Deadwyler of the Bowman Gray School of Medicine, extension of work on the electrophysiology of nicotine to the hypothalamus is proposed. In the second, from Dr. Donald Woodward of the University of Texas Health Sciences Center at Dallas, imaging of brain areas whose metabolism is altered by nicotine is proposed, along with companion studies of the effects of direct introduction of nicotine into the brains of awake, behaving animals. Revised drafts of both proposals are expected shortly.

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2. Blood Chemistry

The gel-breaking procedure for use in the dichloromethane extraction of nicotine and cotinine from plasma continues to be successful. A statistically-designed study of the effects of operator, day-of-week and sample concentration on the recoveries of these compounds from known mixtures is underway. Assuming success in this work, analysis of the backlog of plasma samples from previous experiments will begin by mid-August.

Authentic samples of nicotine fumarate and salicylate, N-ethylnornicotine salicylate and N-eth_-nornicotine fumarate, being prepared by Dr. Tomas Hudlicky at VPI, should be available by mid-August.

3. Psychophysiology of Smoking

A pilot study of the effects of smoking on heart-rates of smokers during social conversations is underway. R&D employee volunteers are participating. Owing to a paucity of female volunteers, the portion of the work requiring female smokers will be completed with paid, ex-house volunteers.

Planning for a study of the inter-relationships among smoking, stress, psychophysiological variables and blood chemistry is well underway. With the help of the Law and Medical Departments, acceptable procedures for the recruitment and screening of ex-house, paid volunteers are being developed. In addition, these Departments are helping in final development of the experimental protocol. It is expected that the study will commence in late August.

Scientific Affairs

- I was informed by Mr. Wayne Juchatz that the Committee of Counsel for the Tobacco Industry had decided that Dr. Joseph Borzelleca would represent the Industry, as its expert toxicologist, in future meetings concerning the additives on which specific information has been requested. Dr. Borzelleca is Professor of Pharmacology at the Medical College of Virginia in Richmond. Dr. Borzelleca was not on the list of toxicologists on which comments were previously requested nor is he one who we would have recommended.

  Presumably, Mr. Chet Wrobleski will arrange a meeting with Dr. Borzelleca and me for the purpose of orientation on additive issues in general and to discuss the background papers we have prepared.

  Dr. Borzelleca will meet with Joanne Lucta, M.D., Director of the Clearinghouse on Smoking and Health, and present the information the tobacco industry has on the three commonly added materials on which our data was requested. It is anticipated that this meeting will not take place until September or later.

- Position papers on eleven additives used by RJR MacDonald were revised for release to Mr. Derrick Crawford, V.P. of R&D for RJR MacDonald. These position papers will be used as a reference source

but will not be released to any government agency or other third party at this time.

- EPA has announced that a special review was being initiated on the insecticide aldicarb, 2-methyl-2-(methylthio) propion-aldehyde-o-(methylcarbamoyl) oxime, also known as Temik, citing its contamination threat to groundwater. EPA officials said that the chemical's two degradation products, aldicarb sulfoxide and aldicarb sulfone, are of toxicological concern because they have long half-lives in soil and also mobile. Wells near treated fields have been found to have concentrations of 10 or 200 part per billion.

  Aldicarb is registered for use on dried beans, cotton, grapefruit, lemons, oranges, peanuts, pecans, potatoes, sorghum, sugar beets, sugar cane, sweet potatoes, and ornamentals to control nematodes, mites, and insects. It is also registered for use on tobacco for control of nematodes and aphids although it is not widely used for this purpose.

  A Toxline search on Temik has been requested.

- A preliminary draft budget was prepared for the Scientific Affairs Division for 1985.

A. Wallace Hayes

A. Wallace Hayes

AWH:bm

cc: Dr. R. E. Morse
Mr. B. V. Hardin
Mr. L. L. Bass
Mr. J. C. Phillips
Dr. D. H. Piehl
Dr. C. E. Teague
Dr. Alan Hodgman
Dr. J. H. Reynolds
Dr. C. W. Nystrom
Ms. S. L. Joudy
Ms. Lori Rust

DEPOSITION EXHIBIT

NOT RECEIVED

DEPONENT: A. WALLACE HAYES (6/3/98)

CASE NAME: People of the State of California

EXHIBIT NO: 4

#5
- Hayes'

Authors: Patrick M. Lippiello
Carl L. Chamberlin

Date: October 30, 1984

Group: Biochemical/Biobehavioral R&D
Division: Biobehavioral R&D

Notebook Pages: 341060-341100
280465-280477

R&DM: 1984, No. 77
No. of Pages: 18

Dated: 9/8/83-5/1/84
8/21/84-8/24/84

Project No.: 7610 - Smoker Behavior

Previous Reports: R&DM No. 14, 1984

DEVELOPMENT AND APPLICATION OF COMPUTERIZED METHODS FOR ANALYZING NICOTINE BINDING MODELS

OBJECT: To define a statistically valid model which describes the binding properties of nicotine in a neuronal cellular receptor system.

SUMMARY: Data from experiments on nicotine binding to neuroblastoma cells were analyzed using statistical curve-fitting methods adapted to a laboratory computer system. The results confirm the presence of two major populations of binding sites in these cells, one possessing a high affinity, and the other a low affinity, for nicotine. The low affinity class represents approximately 95% of the total binding sites in these cells. These results corroborate the two-site hypothesis previously suggested (R&D No.14, 1984).

STATUS: Major data analysis capabilities are complete. Additional modifications to this software are planned to expand data analysis and graphics features, and to improve interactive capabilities.

TECHNICAL ABSTRACT:

An iterative program, based on the methods developed by Munson and Rodbard (Anal. Biochem. 107,220-239), has been adapted to our laboratory computer system to analyze nicotine receptor binding data. Program capabilities provide for data reduction, curve-fitting analysis by a non-linear least squares (Newton-Gauss) algorithm, comparison of binding models, determination and statistical verification of the most appropriate binding model, and calculation of the associated binding parameters (i.e. Kd,Bmax). Graphical representation of the results, in the form of Scatchard, Hill, saturation, and displacement binding plots, is also possible. A unique feature of this software is a normalization procedure which can determine common binding parameters for multiple independent data sets.

To test the software capabilities, six previous nicotine binding experiments with murine neuroblastoma cells/membranes were analyzed simultaneously to determine if all of the data were consistent with a single, statistically valid, binding model and a common set of binding parameters. One, two, and three site models were considered. The analysis confirmed the presence of two independent binding sites, possessing different affinities for nicotine - a high affinity site with a mean Kd of 0.6nM and a maximum number of sites (Bmax) on the order of [illegible] femtomoles/mg protein, and a low affinity site with a Kd of 58nM and a Bmax of 225 femtomoles/mg. These results support the two-site binding model which was previously hypothesized (R&DM No.14, 1984). In addition, the binding parameters determined by the present methods are consistent with those which were originally estimated graphically.

I. INTRODUCTION

A major impediment to the understanding of nicotine receptors in the central nervous system has been a general disagreement among the major laboratories working in this area on some very basic criteria, including the number of sites (Bmax) and their affinity for nicotine binding (Kd). The number of sites which have been reported range from one (1) to as many as five (2). Similarly, Kd values differ by several orders of magnitude, from 0.02nM (2) to 5300 nM (3). Some of this variability can be attributed to differences in methodology and to intrinsic differences among the animal strains utilized. However, considerable variation in parameter estimates can also arise from differences in the methods used to analyze and interpret data. The most common approach has been to estimate binding parameters from Scatchard plots. When a single class of non-interacting binding sites is present, the resulting (linear) Scatchard plot lends itself to straightforward linear-regression analysis and unambiguous interpretation. On the other hand, the non-linear Scatchard plots which are often encountered, particularly in nicotine binding studies, are more difficult to interpret and can be explained by cooperative effects as well as by multiple non-interacting sites. Until recently, most of the methods utilized to estimate binding parameters have been based either on graphical estimates or manual iterative procedures (4-6). Graphical estimates are inappropriate since drawing lines through the points or estimating limiting slopes yields crude approximations, at best. Similarly, errors can occur in iterative curve-fitting procedures which are done manually. A visual assessment of the goodness of fit can lead to erroneous results since the statistically correct (properly weighted) fit is not always the best looking fit to the points. Through the use of mathematically rigorous binding models and computerized curve-fitting algorithms, many of the analytical problems which have plagued ligand binding studies are now being resolved (7-9). The present report summarizes the capabilities of in-house software which has been developed for the analysis of nicotine binding data. It consists of four programs, "SCAPRE", "SCAFIT" "SCAGRAPH, and "INHGRAPH", which have been written in BASIC to be compatible with an HP-86 microcomputer system. These programs have modified and extended the capabilities of "LIGAND", initially introduced by Munson and Rodbard (9), to handle the specific requirements of our nicotine binding studies.

BEST IMAGE

II. METHODS

A. Data Reduction ("SCAPRE")

The data generated in nicotine binding studies describe the binding of ^{3}H-nicotine either to intact cells in vitro or to cell membrane preparations derived from the cells. Experiments must be designed to distinguish between nicotine which is bound specifically to receptor sites from that which is bound nonspecifically. The major sources of nonspecific binding are low affinity tissue sites, either lipid or protein in nature. However, nicotine can also bind nonspecifically either to the glass fiber filters which are used to rapidly separate unbound ligand from membrane bound ligand, or to plastic surfaces on which cells are grown, when binding to intact cells is being monitored. In some cases, ligands have even been shown to bind specifically to inert substances (10). In a typical experiment, controls for

all of these possibilities may be applied. In equilibrium binding experiments with cellular membranes for example, the following parameters are generated from measurements at a series of increasing concentrations of ^{3}H-L-nicotine:

TMB - total membrane binding (^{3}H-nicotine plus tissue)
NSMB- nonspecific membrane binding (^{3}H-nicotine, tissue, and excess unlabeled nicotine)
TFB - total filter binding (^{3}H-nicotine; no tissue)
NSFB- nonspecific filter binding (^{3}H-nicotine plus excess unlabeled nicotine; no tissue)

For in vitro binding to intact cells one can measure TCB (total cell binding), NSCB (nonspecific cell binding), TPB (total plastic binding) and NSPB (nonspecific plastic binding) in a similar manner.

For purposes of curve-fitting and statistical analysis of binding models, the amount of radiolabeled nicotine bound specifically to receptor sites must be known and is calculated as:

SMB (specific membrane binding)=(TMB-TFB)-(NSMB-NSFB) (i)

or SCB (specific cell binding)=(TCB-TPB)-(NSCB-NSPB) (ii)

[If there is no specific binding to the filters or plastic dishes being used then TFB=NSFB, or TPB=NSPB, and these parameters need not be considered in the above equations.]

Raw binding data consist of triplicate determinations, in CPM (Counts Per Minute), of each of the above parameters, for up to twenty ^{3}H-nicotine concentrations. "SCARRE" performs the following functions in reducing the raw data for utilization by "SCAFIT".

1. determines mean CPM (Counts Per Minute) for each parameter at every concentration.
2. converts to DPM (Disintegrations Per Minute) based on known counting efficiency (0.45)
3. determines NSB (nonspecific binding), by linear regression analysis (since nonspecific binding is well below saturation, and thus proportional to ligand concentration).
4. determines TFB and NSFB by linear regression analysis, if there is no experimental evidence of specific binding to plastic or filters.
5. determines SMB or SCB for each nicotine concentration by equation (i) or (ii) depending on the type of experiment.
6. converts DPM to specifically bound nicotine per mg protein (fMoles/mg), based on the known specific activity of the ligand and known amount of tissue per incubation.
7. creates "source" and "output" files (for use by "SCAFIT") which contain bound nicotine levels as functions of nicotine concentration.
8. allows for weighting of data by including a weighting parameter for use in "SCAFIT", based on a polynomial expression for weighting coefficients (see "Data Analysis").

B. Data Analysis ("SCAFIT")

Data analysis is performed by the program "SCAFIT". The capabilities of this software can be summarized as follows:

1. Curve-fitting - Curve-fitting is performed on the untransformed saturation data (i.e. bound ligand as a function of free ligand), utilizing a Newton-Gauss method. This algorithm is based on nonlinear least squares

minimization of the sum of squared deviations of the observed amount of bound ligand from the predicted amount of bound ligand, as follows:

$$SS = \sum_i (Y_i - \hat{Y}_i)^2 \qquad \text{(iii)}$$

Terms in equation (iii) are defined as follows:

SS = sum of the squared deviations
Y_i = observed ligand bound, for the ith data point
$\hat{Y}_i$ = predicted ligand bound, for the ith data point.

The predicted amount of ligand bound is calculated from the following equation:

$$B_T = \sum_j \frac{Kj \cdot Rj \cdot F}{1 + Kj \cdot F} + N \cdot F \qquad \text{(iv)}$$

Terms in equation (iv) are defined as follows:

j=1....n,depending on the number of sites postulated
B_T=total ligand bound
Kj=predicted association equilibrium constant $(nM)^{-1}$
Rj=predicted concentration (Bmax) of jth receptor
F=unbound ligand concentration
N=nonspecific binding constant (either predicted or measured)

Iterations are based on program-revised estimates of Kj and Rj. Final parameter estimates by "SCAFIT" include Kj and Rj values with standard errors, an estimate of nonspecific binding (N) if this is chosen as a variable, the sum of the squared deviations (which can be used as an estimate of scatter) and a "runs" test, based on the signs of the residuals $(Y_i - \hat{Y}_i)$ to determine systematic departures of the data from the fitted curve.

2. Weighting - Inverse variance weighting of points by "SCAFIT" is optional (default weighting assigns equal weight to all points) and can be included in equation (iii) as follows:

$$S = \sum_i W_i (Y_i - \hat{Y}_i)^2 \qquad \text{(v)}$$

Terms in equation (v) are defined as:

Y_i = bound ligand
W_i = 1/variance (Y)
Variance $(Y) = A_o + A_1 Y + A_2 Y^2 + A_3 Y^4$

Normally the variance (Y) is considered to be proportional to Y since this is consistent with the constant percentage error usually seen in ligand binding studies.

3. Multiple Data Sets - Inter-experiment differences in the total number of receptors is not uncommon in ligand binding studies. Therefore, normalization factors can be included in equation (iv) to allow for this variability by setting total binding = $C_K \cdot B_T$ for the kth experiment. If, for example, six data sets were to be compared, six additional variables (C_k's) could be included in the analysis. "SCAFIT" determines values for $C_2 \ldots C_6$ (C_1 is always set =1) which together with the minimization algorithm, normalize all data sets to a single binding curve.

4. Comparison of Binding Models - "SCAFIT" can be used to determine the best fit, within experimental error, to a binding model based on one site or multiple sites. The approach involves testing whether the goodness of fit for a model with additional binding parameters is significantly better than that provided by chance alone. To do this, an F ratio is calculated as:

$$F = \frac{(SS_1 - SS_2)/(df_1 - df_2)}{SS_2/df_2} \qquad \text{(vi)}$$

SS_1 and SS_2 are the residual sums of squares for models 1 and 2 (where model 2 involves additional binding sites); and df_1 and df_2 are the associated degrees of freedom. The criterion for model 2 providing a better fit is whether or not the F ratio exceeds the tabulated F statistic (with df_1, df_2) at the 1% probability level. (For a more detailed discussion, see ref. 10).

C. Graphics

1. "SCAGRAPH" - This program implements graphical representation of the binding data which has been previously stored in a graphics file by "SCAFIT". All graphs are displayed as the theoretical "best fit" for the binding model being considered, with the experimental points superimposed. The following plots are available:

   a. Scatchard plot: [Bound nicotine]/[Free nicotine] vs. [Bound nicotine].

   b. Saturation plot: [Bound nicotine] vs. [Free nicotine].

   c. Hill plot - log [Bound nicotine]/(Bmax-[Bound nicotine]) vs. log [Free nicotine]. The slope of the resulting lines is the Hill coefficient, n. If the Scatchard plot is non-linear, n can be interpreted as follows:

      n=1 multiple independent binding sites
      n<<1 single group of sites with negative cooperativity
      n>>1 single group of sites with positive cooperativity

2. "INHGRAPH" - This program plots data and theoretical curves for inhibition binding experiments, where the binding of a given concentration of radio-labeled nicotine is determined in the presence of increasing amounts of a competitive inhibitor. Curves are based on the following equation:

$$[\text{Nicotine Bound}] = \sum_i \frac{B_{max}\,[\text{Free nicotine}]}{[\text{Free nicotine}] + Kd_i\,\frac{1+[\text{Inhibitor}]}{KI_i}} \qquad \text{(vii)}$$

The terms are defined as follows:

B_{max} = maximum number of sites of a given class
Kd_i = affinity of ith site for nicotine
KI_i = affinity of ith site for the inhibitor

III. RESULTS AND DISCUSSION

The data analyses described here are based on six nicotine binding experiments (TABLE I), utilizing intact murine neuroblastoma cells at 37 degrees C (Data Set E) or membranes derived from these cells (Data Sets A,B,C,D,F). Our earlier results, using manual iterative curve-fitting procedures, suggested that two independent classes of nicotine binding sites are present in these

cells (R&DM No. 14, 1984). In order to corroborate this conclusion the data were analyzed by "SCAFIT".

Initially, normalization coefficients were determined for all six data sets (Table II-A, Column 2). A median data set (D) was arbitrarily assigned a coefficient of 1, assuming that the variations in receptor number between experiments are normally distributed. The coefficients determined by "SCAFIT" for the other data sets represent the fraction of receptors present in a given experiment, relative to set D. This can be seen by examining the Scatchard curves calculated by "SCAFIT" (Figure 1). These curves are theoretical fits to the individual data sets, based on a two-site model. In ligand binding studies the plots generated from separate experiments usually form such a series of congruent curves as a result of uniform variations in numbers of receptors (Bmax) and invariant binding affinities (Kd). Normalization of all data sets to a single curve is achieved by multiplying the experimental values for the amount of ligand bound at each nicotine concentration by the inverse of the normalization coefficient. "SCAFIT" does this automatically when a data file is created for the pooled data from multiple experiments.

In order to examine the statistical validity of assigning a single set of binding parameters to all six data sets, each data set was first fitted to a two-site model, with all five parameters (two Kd's, two Bmax's, and a normalization coefficient) held fixed and equal to those determined for the total pooled data. Each of these fits was then compared statistically to the best fit achieved with the binding parameters treated as variables. The results are presented in Table II-A. In every case except one (Set E), there was no significant improvement over the common fit. Although the % rms scatter about the individually fitted curves was lower, the P values were quite high, ranging from .07 to .337. Thus, assigning four binding parameters to each data set (24 in all) is not necessary since the data are adequately described by a single fit to the pooled data. This requires only ten parameters, four common binding parameters (Kd's, Bmax's) and 6 normalization coefficients

To test the validity of a two-site model, "SCAFIT" was used to fit the data from each experiment to a one-site model. Each fit was compared to a two-site fit in which the Kd's were fixed at the values determined for the pooled data (Table II-B). The one-site model did not provide a statistically better fit for any of the six data sets at the P<.05 level (Table II-B, last column). The appropriateness of a two-site model to describe these data becomes even more evident when a statistical comparison is made of the pooled, normalized data from all six experiments. The results are shown in Table III. According to "SCAFIT" the two-site fit (n=33, df=24) is better than a one-site fit at the P=0 level.

In order to rule out the possible presence of additional sites, "SCAFIT" was used to compare a three-site to a two-site model (Table III, last two columns). Clearly, within experimental error, the two-site fit is better. The additional parameters of the three-site model provide a better fit by chance about 40% of the time. The standard errors associated with the predicted binding parameters, expressed as a percentage of the mean, reflect this result as well, ranging from 84% to 632% (See Table III, last column).

It should be noted that the efficiency of the "SCAFIT" software in accurately describing appropriate binding models/parameters depends strongly on user intervention. This can be seen from the results presented in Table IV. Although fits 2-5 all provide descriptions of the data which are statistically more accurate than the manual method (fit No. 1), there is considerable disparity among the calculated binding parameters. This results from differences in weighting and/or nonspecific binding parameters, which are both predetermined by the user. For example, nonspecific binding is allowed as a variable only when it has not been experimentally determined by "blank" incubations. Similarly, the choice of the best weighting model will depend on the intrinsic error properties of the system. In most binding studies, a constant

percentage error in the dependent variable (i.e. ligand bound) is assumed (see "Methods", B.2). In the present studies N1 is fixed at zero since nonspecific binding is experimentally determined and is already corrected for in the data. The inverse of the variance (V) was chosen in weighting the data, where V(Bound)=.01 (Bound), which is valid for the experimentally observed error range.

Graphical representations of the pooled data, together with the best theoretical fit determined for a two-site binding model, are shown in Figures 2 and 3. The presence of the second (low-affinity) site, which is not readily seen from the saturation curve (Figure 2), is clearly illustrated by the biphasic nature of the Scatchard plot (Figure 3). The "goodness of fit" is visually apparent. The mean %rms scatter of the data about the fitted curve is ±7.4%. The presence of two independent sites is further confirmed by inspection of the Hill plot (Figure 4), since the slope is close to unity. Cooperative effects within a single class of sites, when present, result in slopes less than 0.5 (negative cooperativity) or greater than 2 (positive cooperativity).

IV. Conclusions

The results from "SCAFIT" analyses provide statistical confirmation of a two site model to describe the binding of nicotine in a model neuronal cell system. The binding parameters (Kd, Bmax) determined for these sites are in the same range as those reported for other neurotransmitter receptor sites in brain. These results support the use of the in vitro neuroblastoma cell model for further studies of the binding of nicotine to neuronal cells and of the possible receptor-mediated biochemical consequences of this binding.

Patrick M. Lippiello

Carl L. Chamberlin

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Dr. G.T. Burger

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Hayes 6

REC'D JAN 9 1985 Miller

RJR Interoffice Memorandum

Subject: Trip Report - Council for Tobacco Research, New York, New York - December 13-14, 1984

From: G. T. Burger

To: Dr. A. W. Hayes:

Date: January 7, 1985

Drs. A. Wallace Hayes, G. T. Burger, and Leon Goldberg met with Dr. Sommers and another gentleman representing CTR (Council for Tobacco Research) and Ed Jacob, Attorney at Law, on Thursday afternoon, December 13, to discuss the chronic mouse study conducted at Microbiological Associates Contract Laboratory. Items in the report which were discussed included: writing style that left some paragraphs easily interpreted several ways; high mortality of animals in first chronic study; depiction of restraint of laboratory mice such that overt stress is implied; confusion over dosimetry issues; dose of 1 mg. TPM per mouse roughly equals 250 cigarettes a day in man and not typical of the average smoker or even the heavy smoker; and need to publish as a series of articles in refereed journals the information found in this study. As a solution to those concerns, Dr. Hayes suggested that a "ghost writer" be hired to expedite the completion of the manuscript for publication. This person could help Dr. Carol Henry get the articles in an acceptable format but allow Dr. Henry to put her own interpretation on her data. In other words, this person would help Dr. Henry write the articles but not attempt to influence her interpretation of the results of the experiments. It was felt by all of those present that this study needs to be presented to the scientific community in lieu of the results. Dr. Sommers agreed that this would be helpful but due to CTR's policy regarding publications and investigators that CTR should not be involved any further in putting pressure on MA to publish their results. Therefore, it was suggested that R. J. Reynolds might hire such a ghost writer. Of course that would mean that R. J. Reynolds would be acknowledged as providing financial support for preparation of manuscripts. As long as R. J. Reynolds did not dictate or influence the author's interpretation of data, there should not be a problem with this approach. The meeting closed with everyone agreeing that a consultant hired to help organize the manuscripts would be a feasible approach to successful publication of MA's work.

Drs. Burger and Hayes attended the annual meeting of the board of CTR on Friday morning, December 14. They were introduced to members of the board and attending audience. The financial statement was reviewed and two speakers gave overviews of their work that was supported either by CTR or tobacco companies. Dr. Barry Pierce presented his work on "humoral" control of cell growth both in embryos and in neoplastic tissue. His laboratory in Colorado is largely supported by R. J. Reynolds grants.

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The trip was very informat ve and gave me more insight as to the scope and activities of CTR.

G. T. Burger

/lcf

#7

REC'D JAN 10 1985 Miller

MICROBIOLOGICAL ASSOCIATES INC.

Microbiological Associates Inc
5221 River Road
Bethesda, Maryland 20816
(301) 654-3400
Telex 90-8793

A Subsidiary of
Daryl Laboratories Inc

January 8, 1985

Dr. A. Wallace Hayes
R. J. Reynolds Tobacco Company
401 Main Street
Winston Salem, North Carolina 27102

Dear Dr. Hayes,

Enclosed is an outline of the position paper entitled "Approaches to Toxicological Evaluation of Whole Tobacco Smoke", which Dick Kouri, Ray David, and I have put together. All of these approaches involve inhalation of whole tobacco smoke in model animal systems. A second position paper may be required to address the toxicology of tobacco smoke condensate material.

Also enclosed is the draft outline of the monograph for IARC (International Agency for Research on Cancer) entitled "Tobacco Smoking". The meeting to assemble this monograph is to be held in Lyon, France, on February 12-20, 1985, and Dick is an invited participant. In preparing for this meeting and in preparing another manuscript for publication, we feel we have a good start toward addressing the approaches outlined for the position paper. Dick will also provide his own summary of the IARC Meeting. Both the position paper and Dick's summary should be ready by March 31, 1985.

We have estimated that it will require 240 hours of professional and secretarial time to complete these projects. Curricula vitae for the professionals who will work on this project are enclosed. Dick will act as a consultant to MAI specifically for this project. The total cost will be $24,000.

If this proposal meets with your approval, please acknowledge at your earliest convenience. Dick can be scheduled to spend a majority of his time on these projects commencing January 14, 1985.

Working outlines for manuscripts from the CTR Projects are being sent under separate cover.

Sincerely yours,

Carol J. Henry

Carol J. Henry, Ph.D., D.A.B.T
Director, Inhalation Toxicology

CJH/ph
Enclosures

RJRT/TEXAS AG

BEST IMAGE

Hayes # 8

RJR Interoffice Memorandum

Subject: Microbiological Associates
Draft Report Discussion

Date: June 12, 1985

To: Dr. A. W. Hayes
Dr. R. L. Suber

From: G. T. Burger

As you have requested, I have reviewed the document prepared by Microbiological Associates on approaches to toxicological evaluations of whole tobacco smoke. There are two attachments to this memorandum: (1) List of General Comments Regarding the Scope of the Document and Specific Areas that Need to be Addressed, and (2) Specific Areas that Need to be Omitted or Modified. Before discussing the general comments and the specific areas of criticism, I would like to call your attention to one general deficiency of this document. There should be attached to this document a preface or introductory letter that makes it very clear what the scope of this draft should be. This will help the reader (whether it be a day or 10 years from now) understand the entire purpose of this document. That preface should state that this document represents Dr. Henry's and others at Microbiological Associates view on how to approach the toxicological evaluation of whole tobacco smoke. This is not RJR Tobacco Company's view but rather it is Microbiological Associates' way of approaching the problem. Also in discussing the goals of this document I think they should stick to what I see is the intent of the document. That is, they should limit their discussion to a review of the animal research in tobacco smoke with very little reference to epidemiology studies. Additionally they should introduce the second volume as examples of protocols that they would follow while conducting tobacco research. By making this very clear in a preface document it should represent a much more acceptable document for the Toxicology Research Division. In closing I would like to add that I do not agree with many of the approaches suggested by these authors nor do I expect to have to follow their protocols or their guidelines. It is obvious to me that the authors of this document do not understand the complex issues facing the tobacco industry. The simplistic idealistic approach to tobacco smoke research that they suggest is cumbersome, expensive, and in my view unnecessary for evaluating new products. Therefore, the preface document should include statements to the effect that this is how they, the scientists that wrote this document, would approach this problem. Also attached are critiques from two members of the Toxicology Research Division that you may find useful. If either one of you have any questions regarding this critique, please feel free to contact me.

G. T. Burger

/lcf

Attachments

JUN 13 1985 SLJ

ATTACHMENT I - GENERAL COMMENTS TO THE DRAFT DOCUMENT ENTITLED "APPROACHES TO TOXICOLOGICAL EVALUATION OF WHOLE TOBACCO SMOKE"

In reviewing the document prepared by Microbiological ociates I feel compelled to make several general statements or comments regarding the content of this document. This document seems to suffer from a lack of clear focus as to the intent of the document. Many areas are visited by the authors including epidemiology and philosophical points of view regarding "safe cigarettes" and protocols that represent the authors point of view of study design. Therefore, listed below are several general comments that will help make the document focus more clearly on a goal and make it more useful for R. J. Reynolds.

1) A preface or introductory statement is needed that clearly outlines the intention of this document. Such a statement should make it very clear that this is not a R. J. Reynolds document but rather a Microbiological Associates document prepared for R. J. Reynolds outlining the opinions of the scientific staff of Microbiological Associates concerning tobacco smoke research.

2) Much of the "flavor" of this document appears to be self-serving rather than objective. The discussion frequently leads to a conclusion that the smoking machine or the techniques used by Microbiological Associates are the best ones available. I believe this detracts from the quality of the manuscript and such self-serving kinds of statements whether intentional or not shoul be avoided.

3) The reader is not clear whether this draft document represents a position statement, a review of the literature, or a research proposal prepared by a contract laboratory. It has characteristics of all three. It is my feeling this document should represent a review of the animal research and <u>in vitro</u> research and that this document should avoid encapsulation or summaries of epidemiology studies. In addition, this document should curtail some of the philosophical remarks that are included throughout the discussion.

4) Regarding the references to epidemiology studies, the authors' approach to epidemiology, a very complex issue, uses only selected papers. One wonders whether or not the authors did an extensive literature review on epidemiology or rather take from other documents a few selected studies. If a selection process was undertaken, it would be helpful to know how they chose which papers to review. Many of the papers presenting conflicting results as to the association of tobacco smoke and selected diseases are not represented here. Furthermore, R. J. Reynolds has a position on smoking and health, and also has a department that addresses these issues; therefore, it is not the intention, in my opinion, of this document to address those issues. If this document remains as written, it could represent conflicting or confusing points of view that would create unnecessary problems for the Biochemical/Biobehavioral Group. I suggest that references to epidemiology studies should be removed from this document.

5) The tables in the back of Volume I and the Draft of Volume II referred to as Appendices A and B represent useful information for comparison purposes to the staff of Toxicology Research Division. In fact these areas represent the most useful information to us. Some how, either in the preface document addressed in Point 1 above or as a prelude to the appendices, it should be made clear to the reader that these are protocols suggested by the contract laboratory, Microbiological Associates. Therefore, these protocols would not come back to haunt us later. However, they do represent a nice resource or comparison of approaches for the Toxicology Research Division staff and should be left as part of the documents or alternatively submitted as an independent document.

6) Much of the discussion centers on smoking and health issues and not on biological activity assessment and comparisons. It is my view that the scientific community has not yet found a model or models that adequately address smoking and health issues. This is understandable due to the complexities of the issues. The nature of this document suggests but does not state that models are presently available and acceptable. The authors should clarify their opinion regarding the utility of the models presently available.

7) The remarks on future directions are essentially useless. Either subjects such as oncogenes should be addressed in-depth or not mentioned at all.

ATTACHMENT II - SPECIFIC CRITICISMS ON THE DRAFT DOCUMENT ENTITLED "APPROACHES TO TOXICOLOGICAL EVALUATION OF WHOLE TOBACCO SMOKE

Writing style and grammatical corrections are entered within the document and will be sent to Dr. Suber. However, content or specific points that I feel need to be addressed, reworded, or omitted are listed below (listed chronically by page number):

1) Under Introduction, Page 3 - the first paragraph: The last sentence of the first paragraph should be omitted because it is speculation. This should be omitted unless considerable more discussion is going to be included.

2) Page 5 - Section two: The last sentence on the page should be reworded or omitted. It should be reworded to state whether or not baboons, which are used in cigarette smoke research, actually inhale. It my understanding that baboons puff rather than inhale cigarettes, and therefore, are not adequate laboratory models.

3) Page 6 - First line: I am not certain that these dogs have been trained but rather forced to accept smoke through tracheostomy tubes. The sentence implies that dogs not only tolerate but may even voluntarily accept tobacco smoke. It was my understanding that this was a forced inhalation sort of study. I may be wrong, but it needs to be addressed as an issue.

4) Much of the discussion regarding smoke aerosol generation and smoking machines appear to be self-serving and indicate that the techniques used by Microbiological Associates are far superior to those commercially available. I believe this sort of approach detracts from the objectivity of this document and should be avoided.

5) A considerable amount of information is presented on smoking machines. It implies that the SEMII machine used by Microbiological Associates is the best machine available commercially. I doubt that this is the case by talking with the investigators from other laboratories, and I'm a little bit skeptical about the claims made by Carol Henry's group regarding this machine for a variety of reasons. However, in any case I think to present a discussion of this sort to imply that the SEMII is the most advanced machine available requires a great deal more information than is presented here to prove the superiority of that machine. Therefore, I recommend that the discussion of different machines be condensed somewhat or at least reworded such that it doesn't sound like an advertisement for the SEMII machine. One of the faults of the SEMII is the maintenance problem. Other investigators have indicated that it is hard to keep this machine running and is very cumbersome to operate and labor intensive. This is not strongly presented in this particular document which brings to question the objectivity of the whole smoking machine discussion presented in the document.

6) Page 12 - The first full paragraph begins - Aerosol characteristics are good with this machine and nearly 90% of the TPM is delivered to

the animals. They're discussing the Maddox machine. I would like to know what good aerosol characteristics are. Why are they considered good? Are they good because they are identical or comparable to main stream smoke? In other words, what is the criteria for saying aerosol characteristics are good. What do the authors mean by that statement?

7) On Page 13 the authors present the question of methods of exposure of animals to cigarette smoke. The various kinds of machiner and devices are listed; however, one of the problems with the stockade-type animal holder used by Microbiological Associates, referred to as a stock holder, is how many animals die during the conduct of a chronic animal study. This is not brought out very strongly here in this discussion but yet it is a well known problem or drawback to this animal holder device.

8) Page 15: At the top of the page the authors discuss the stress of restraining animals and relate it to plasma corticosteroid levels referring to a paper by Deturck et. al. 1980. I have not read this article; however, it is my feeling that corticosteroid plasma determinations alone are too erratic to be used as a parameter for measuring stress. These sorts of blood concentrations, corticosteroid, have to be taken into account with a variety of other parameters including histopathology (adrenalitis, etc.) before one can build a case for stress. But corticosteroid levels alone in the blood are, in my experience, unreliable indicators of stress.

9) The discussion of radiolabels is very good and for the most requires no modification. I would, however, like the authors to discuss the feasibility of carboxyhemoglobin levels to indicate delivered dose of cigarette smoke. Is it reliable and fairly reproducible for levels of carbon monoxide or level of aerosol and particulate delivery to the lung of cigarette smoke or is it not reliable. More discussion needs to be brought forth regarding that measurement.

10) Page 21 - The authors mention measuring the smoke particulate generated from a cigarette: Methods utilized to measure particulates need to be discussed more in-depth. It is my understanding that aerosol particulate measurements have been crude measurements in the field until recently and recent advances have greatly improved aerosol particulate measurement concentrations. So the authors should discuss methods of measurement both of particulate size or types of aerosol; methods they feel may be useful. Then we should, after receiving this information, refer it to Charlie Green and his people to evaluate for technical quality and feasibility.

11) Under Section B - Subchronic Inhalation Studies - bottom of Page 23: The last paragraph discusses that chronic exposure to tobacco smoke frequently leads to a longer life for the animals. It relates this observation that weight gain is general less in these animals; and therefore, the weight gain is an unhealthy property for an animal and could cause "disease". I think this a point well taken, but that paragraph needs to be reworded so that the discussion is more plainly understood by the general reader.

12) Page 24 - At the bottom of the page a statement is made that organ weights have not been routinely monitored in animals exposed to cigarette smoke. I was under the impression that organ weights, particularly lung and brain, were frequently used as parameters in cigarette smoke research. It's merely a question if the authors still feel this is the case, then I guess there are no changes to be made; but is that really true. It is ironic that they go on in the rest of this paragraph and talk about organ weight data in the literature.

13) Page 26 - Under Item 6 - Histopathology, etc., in the first paragraph the authors state that in hamsters some evidence of laryngeal papillomas were observed - they're citing a paper by Walker, et al. The authors should say what they mean by some evidence. Are these truly papillomas or are they papillomatous hyperplasia or were there such a low number of papillomas that the authors aren't sure as to what it may mean. In other words, they need to clarify what some evidence indicates. The next sentence after that - says the pulmonary tissue of dogs showed evidence of fibrosis and emphysema. Again I'm not sure what they mean - "showed evidence". The lungs were either fibrotic and emphysematous or were not. Some evidence is a phrase that I don't understand - it's like quantifying a qualitative parameter. It does not make sense as stated.

14) Page 27 - Under Chronic Inhalation Studies: It is very disappointing after wading through many pages of discussions regarding subacute and acute studies that chronic inhalation studies are summed up in one paragraph and a short paragraph at that. I feel very strongly that chronic inhalation studies should be one of the most in-depth discussions held in this paper. The authors state that there is good information in two recent reviews, Pepelko and IRAC. My feeling is that if we had wanted the information presented in those two articles, we would not have had them produce this position paper. I don't know whether it was intentional or not, but abbreviating this informative paper is unacceptable in my mind.

15) Under Metabolism of Cigarette Smokers a great deal of information is given on a wide range of enzymes and metabolites in the discussion on such things as cyclic GMP and prostaglandins; however, pertinent information regarding tobacco smoke should center around such issues as production of acrolein, nicotine metabolism, nitrosamines, polycyclic aromatic hydrocarbons, etc. Some of this information is discussed; however, I was disappointed in the nicotine, acetaldehyde, and acrolein discussions; either by the lack of discussion of these compounds or the brevity of what discussion was present.

16) Page 38 - the end of the first paragraph where it talks about macrophages from smoke exposed rats and then goes on to say contradictions in the literature may result from the instability of isolated PMN's. I think that needs to be corrected to PAM's (Pulmonary Alveoli Macrophages) and not PMN's. Otherwise, the two sentences do not relate to each other.

17) Page 39 - last paragraph - second sentence - Genic Stimulation: I don't know what that means and I suspect that most people don't. It's either a misspelling or needs to be defined. The last sentence

in that paragraph uses the word worn out surfactant. Perhaps the word depleted, degenerated, surfactant, or something of that sort - I don't know if surfactant can be worn out. Another adjective needs to be used other than worn out surfactant.

18) Page 42 - last sentence on the page continuing on page 43 - this sentence presents the theory of the elastase and the elastase inhibitors ratio being unbalanced in certain diseases: The authors needs to state that this is a hypothesis and hasn't been proven yet, but has attracted a lot of investigators. I happen to agree that it's an excellent hypothesis, but it still a hypothesis as they have indicated and some further comment about it being a hypothesis that has yet to be proven would be worthwhile. Perhaps that's addressed adequately in that main paragraph but the whole paragraph should be reworded in such a way that the naive reader understands that it is one of the most popular hypothesis but still has not been proven.

19) Page 43 - middle paragraph: I'm not real sure what this paragraph means. The author should explain the sentence in more detail or leave the sentence out altogether. It appears to be a thought tagged on at the last moment. I think it is good to state which enzymes they're discussing. So it needs to be amplified or it needs to left out altogether.

20) Page 46 - last sentence of the first paragraph - These results suggest measurements of enzymes, etc., serve as an indicator of potential tobacco smoke toxicity: I would change that to state indicator of tobacco smoke biological activity. Toxicity, particularly in reference as to how it is used here, is an ill chosen term. When you talk about beta-glucuronidase and gamma-glutanyl-transpeptidase being increased, that's not necessarily a toxicity change or indication.

21) Page 48 - A great deal of discussion is given to gene sequences and DNA techniques: The discussion is interesting but it needs to be more specifically discussed regarding tobacco smoke. In other words, are they talking about interaction of DNA and tobacco smoke. The authors have made the statement that newly defined recombinant DNA techniques make it quite feasible to characterize the genetic structure. In my opinion we are discussing hundreds of thousands of dollars worth of research here. I don't believe we yet know enough about the structure of DNA in regards to toxic lesions and the recombinant DNA techniques to make it useful in tobacco smoke research. I may be wrong. The same is true, in my opinion, of oncogenes. Therefore, the authors needs to explain exactly how they would attack this issue or not bring it up at all. As it is now stated, they simply open "Pandora's Box of Problems" without specific approaches that they would undertake in order to the study the effect on DNA. This leaves us with a dilemma that is not necessary. Either the authors should not approach this area at all in their discussion or be very specific on how they would utilize this area of research.

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22) Page 49 - under Immunotoxicity - second paragraph - third sentence: The sentence ...cells play a vital role should be reworded. The sentence structure makes it very hard for me to comprehend exactly what the authors mean by this statement.

23) Page 50 - under Metabolism: This paragraph is filled with "maybe" kinds of statements - maybe, maybe, maybe. I'm not sure that AHH is a fruitful area of endeavor for tobacco research. It has certainly disappointed many investigators as to it's implication for cigarette smokers. However, the authors present some bothersome claims regarding mutagenic events and induction of placental AHH and what that effect may be on fetal growth and development. As stated here it presents real problems for me.

24) Page 51 - under Reproduction and Teratology: The seventh sentence states these results suggests that the effect is directly on the testes. I assume they mean to cause spermatids were reduced and primary spermatocytes were abnormal that somehow proves that the effect is directly on the testes. I think I know what they mean but is it defensible statement. How can one eliminate or discard the hypothalamus and pituitaries being involved. In other words, as a Pathologist, I know what they're implying, but many people reading this part of the paper would not understand what the authors mean.

25) Page 54 - Cardiovascular Toxicology: The authors in the first paragraph, by saying that this is a complex area because of known cardiovascular effects of constituents of cigarette smoke, such as nicotine and carbon monoxide - what are the known cardiovascular effects? Are the authors talking about physiological effects or pathological effects? Because pathological effects of nicotine and carbon monoxide as found in cigarettes are not known to have specific cardiovascular lesions. If it is the case - if there are known lesions due to nicotine and carbon monoxide, the authors needs to explain what those are. In other words, this seems to me to be a statement that is unsupported by the scientific literature.

26) Page 55: Myocardial changes are mentioned that are probably due to carbon monoxide, but they are not described. If the paper, such as the study by Lough is presented, the authors should tell what those changes were.

27) Page 56: The first paragraph of that page needs to be reworded. It's difficult for the reader to understand it. The sentence - changes in the heart and cardiovascular system, etc. - precedes discussion of inflammatory changes. I don't understand the entire discussion here; first they say there are changes and they're inflammatory and then the authors end with no significant differences in the incidence of vascular disease. Arteritis is a vascular disease and they say that was observed. I'm not sure what that means, so the whole paragraph needs to be reworded.

28) Page 56 - the second paragraph: The authors state there's no significant difference found in plasma clotting time in rats. Then the

authors go on to talk about hypercoagulability in old rats and clotting time of plasma being prolonged. These are significant differences in plasma clotting time. Then the next sentence says there was a significant shorting of plasma clotting time, so was there or was there not a difference in plasma clotting time in this study by G ccraa eo x755,

29) Page 58 - A discussion is presented on recommended approaches: There are several statements in this whole area that bother me as the reader. The authors make the statement that it's not possible to find a suitable animal model that would reflect the effects of unsafe cigarettes. Yet they have spend pages of discussion talking about so-called toxic effects or lesions of tobacco smoke. But here they make the statement that developing a safe cigarette by use of an animal model is not possible or not useful at this time. I don't believe we wanted the authors to state whether or not it's possible to evaluate a safe cigarette. We wanted the authors to make an assumption that it is possible, and how they would go about it. Apparently they have met this particular charge simply by saying it's not possible or useful at this time. I have a great deal of trouble with that approach. Then they go on to talk about a quality control cigarette and discuss that at length. It seems to me that one has to define what we mean by safe and I agree with the authors contention that there are no good lab animal models and it would be difficult to prove a cigarette is a safe cigarette. I think the discussion presented for the quality control cigarette was more of what Dr. Hayes had in mind when he asked them to discuss how to test a "safe cigarette".

30) Page 64 - Under Duration of Dosing: They've already talked about using hamsters and rats as a model, but now they're talking about sacrificing animals at 18, 24, and 30 months. Thirty months would not be very feasible for hamsters, and if rats are stressed, it may even be hard for rats to live 30 months under a test regime.

31) Page 66 - Under Synergism Between Smoke and Other Factors: The authors address an area of considerable controversy and difficulty regarding research. It is my feeling until more specific information is forthcoming on direct effects on cigarette smoke, whatever they may be, before one can really address synergism and other factors in an intelligent way. Therefore, this area may be better not to discuss at all.

32) Page 67 - the first sentence states - human epidemiology data suggests an overwhelming relationship between cigarette smoking and lung cancer. I would reword it to say, a strong association between smoking and lung cancer or a significant association.

This concludes some of the more pertinent specific suggestions I have regarding the Microbiological Associates' draft report. Other suggestions are in the manuscript.